VOLUME 100 • OCTOBER 1957 • NUMBER 4

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INTERNAL MEDICINE

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Harry F. Dowling

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The History of the Use of Iodine in Toxic Diffuse Goiter (Graves' Disease)
Arthur L. Bloomfield

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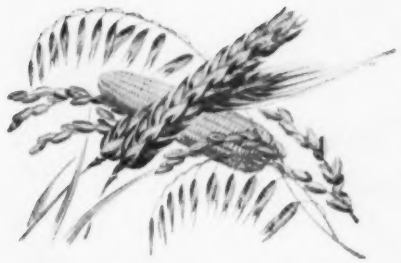

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Bowes, A. deP., and Church, C. F.: Food Values of Portions Commonly Used. 8th ed. Philadelphia: A. deP. Bowes, 1956.
Cereal Institute, Inc.: The Nutritional Contribution of Breakfast Cereals. Chicago: Cereal Institute, Inc., 1956.
Hayes, O. B., and Rose, G. K.: Supplementary Food Composition Table. J. Am. Dietet. A. 33:26, 1957.

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* Smith, J. A., *J. A. M. A.*, 162:784, May 30, 1953.
Brown, W. T. and Smith, J. A., *South. Med. Journ.*, 46:562, June, 1953. Smith, J. A., *Postgrad. Med.*, 16:316, Oct., 1954. McCullagh, W. H., *Journ. Florida Med. Assn.*, 41:715, Mar., 1955.

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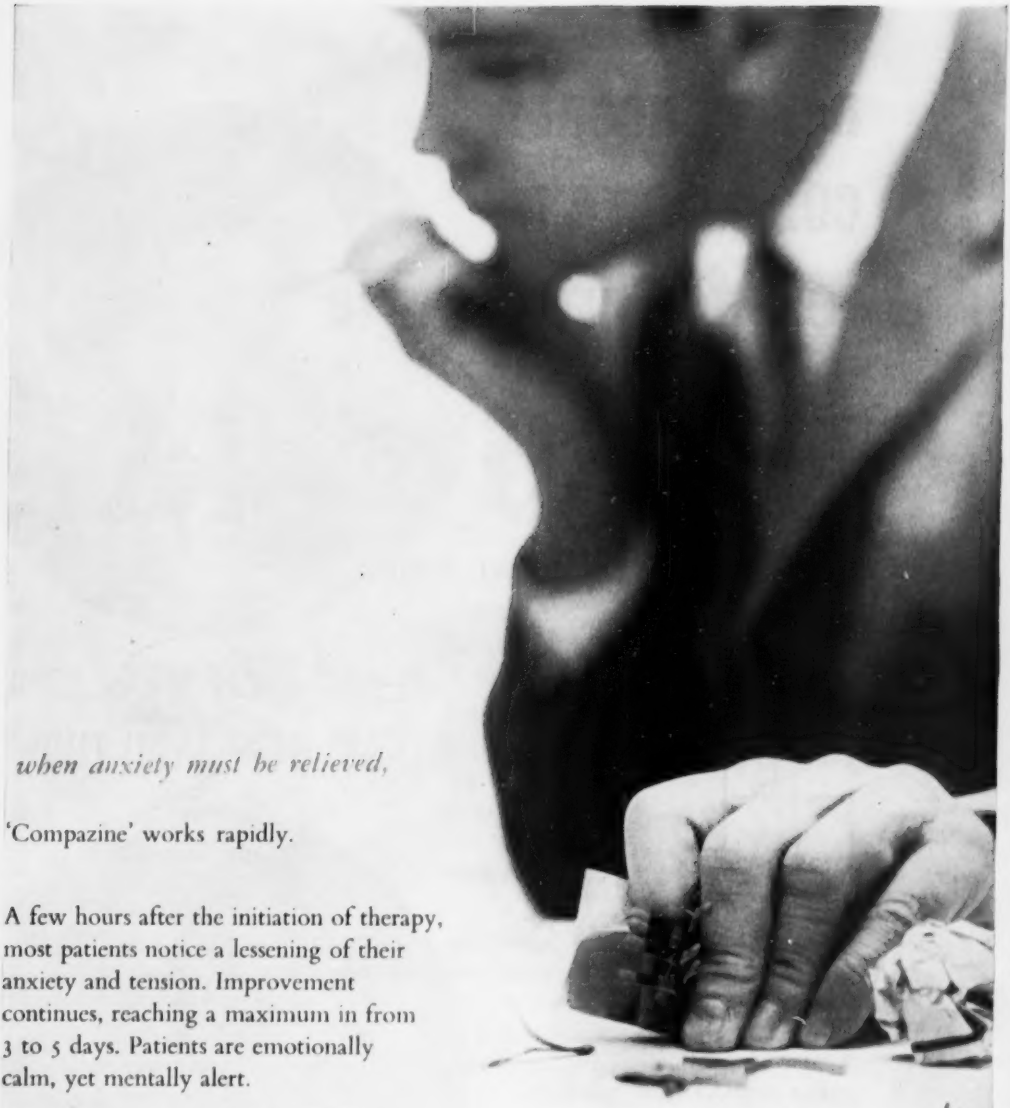

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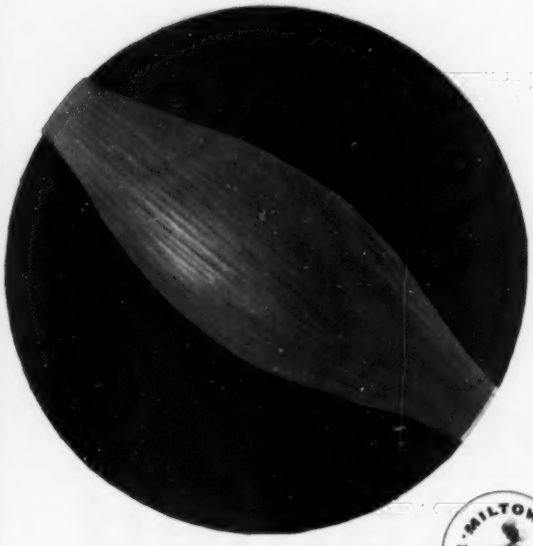

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[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

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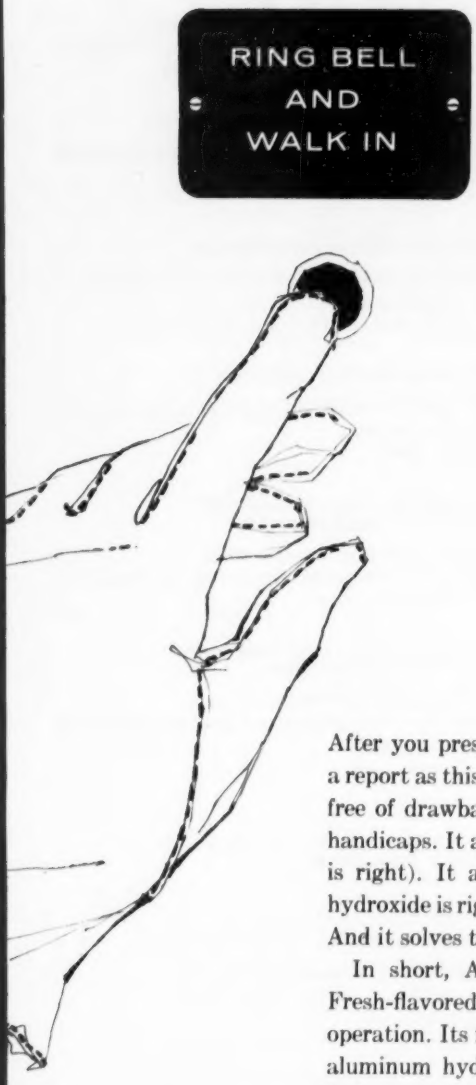

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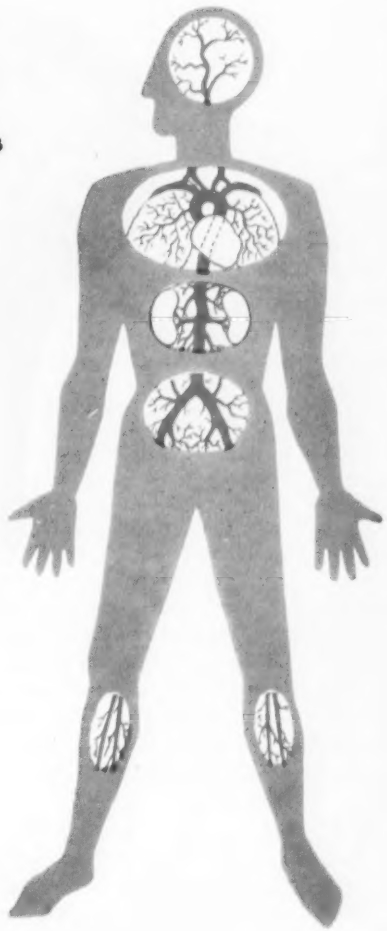

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INTERNAL MEDICINE

Senility

Its Nature, with Some Thoughts Concerning Treatment and Prevention

CHARLES D. ARING, M.D., Cincinnati

There is nothing which for my part I like better, Cephalus, than conversing with aged men; for I regard them as travellers who have gone a journey which I too may have to go, and of whom I ought to inquire, whether the way is smooth and easy, or rugged and difficult. And this is a question which I should like to ask of you who have arrived at that time which the poets call the "threshold of old age"—Is life harder towards the end, or what report do you give of it?

I will tell you, Socrates, he said, what my own feeling is. Men of my age flock together; we are birds of a feather, as the old proverb says; and at our meetings the tale of my acquaintance commonly is—I can not eat, I can not drink; the pleasures of youth and love are fled away: there was a good time once, but now that is gone, and life is no longer life. Some complain of the slights which are put upon them by relations, and they will tell you sadly of how many evils their old age is the cause. But to me, Socrates, these complainers seem to blame that which is not really in fault. For if old age were the cause, I too being old, and every other old man, would have felt as they do. But this is not my own experience, nor that of others whom I have known. How well I remember the aged poet Sophocles, when in answer to the question, How does love suit with age, Sophocles,—are you still the man you were? Peace, he replied; most gladly have I escaped the thing of which you speak; I feel as if I had escaped from a mad and furious master. His words have often occurred to my mind since, and they seem as good to me now as at the time when he uttered them. For certainly old age has a great sense of calm and freedom; when the passions relax their hold, then, as Sophocles says, we are freed from the grasp not of one mad master only, but of many. The truth is, Socrates, that these regrets, and also the complaints about relations, are to be attributed to the same cause, which is not old age, but men's characters and tempers; for he who is of a calm and happy nature will hardly feel the pressure of age, but to him who is of an opposite disposition youth and age are equally a burden.

The Dialogues of Plato: Vol. II. The Republic, translated by B. Jowett, New York, National Library Co., n. d., pp. 3-4.

While it appears that society is doing everything possible to increase the numbers of old people, the orientation of our culture is such as to break down the adjustment of these same people. There can be little question that this potential reservoir of achievement is largely neglected. The statistics reveal that many of them flounder.[12] In 1950, eight and one-tenth per cent of our population consisted of persons 65 and over. At the same time they constituted 25% of the population of mental hospitals. From 1904 to 1950 the number of persons 65 and over in the population increased some four times, while their numbers of first admissions to mental hospitals rose approximately nine times. Neither the improvement in medical care nor the expected increase in the number of older persons developing psychoses due to their longevity explain the phenomenal increase in mental hospital admissions of people over 65.

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From the Department of Neurology, University of Cincinnati College of Medicine and the Cincinnati General Hospital.

It is of interest to contrast the consideration given age in two cultures, the Japanese and our own. In Japan [2]—and this was prior to the imposition of some of our methods—infancy and old age secure maximum freedom and indulgence; restrictions are slowly increased after babyhood, until having one's own way reaches a low just before and after marriage. This low continues for many years during the prime of life, but the arc gradually ascends again until after the age of 60; men and women are almost as unhampered as little children are. In the United States we stand this curve upside down. I wish that we had the rates of senility in these cultures, but I know of no reliable statistics.

In this country, unlike Japan, aging brings gradual isolation. Our young culture is concerned mainly with activity and movement, and stragglers are not too subtly abandoned. Later years bring changes which threaten emotional health, such as physical decline, loss of erotic values, loss of supportive figures, social and economic insecurity, and the gradual contraction in flexibility of adaptive mechanisms. However, I want to point to the loss of hope as particularly endangering the adaptive capacities. The mind then throws up defenses, such as exclusion of stimuli, rigidity, and regression. The aging person clings to familiar patterns of behavior no matter how faulty they are, and new situations evoke irritability, hostility, and resistance by whatever means or symptoms.

Since this problem concerns every one of us personally sooner or later, it ought to be of general interest. Such interest, particularly in scientific company, induces a search for cause. Perhaps oftener than not the physician proceeds as though the phenomenon were due to a single cause, rather than to many. I don't see how senility can be analyzed by an "either-or" approach, regardless of the frenzy with which sides be joined. It may, I believe, be reasonably well understood from the standpoint of the modern pluralistic approach, which considers disease as an adaptation in a continuing equilibrium between organism and environment. In the short cuts of practice—office or hospital—we tend to neglect one or another causal facet, which usually turns out to be the internal emotional environment. I should venture that this technique dedicated to time-saving has been mainly responsible for the devastation of these older persons. Since the internal emotional environment may be a climate as unfavorable or as dangerous as that of a jungle or battlefield and since it often enough is the only avenue of therapeutic approach, it may not be ignored for any reason.

Aging as it relates to the nervous system is accompanied by slowed learning, greater rigidity about what one knows, with less willingness to shift views. There usually is a decrease of recent memory. There is reduction in acuity on the sensory side and of speed and strength on the motor side. We know that senility and old age are not quite synonymous; the former implying a pathological state. However, there is a tendency in our brash young culture to crowd aging people and to refer to them in terms not especially complimentary. Naturally I know more about this phenomenon as it applies to medicine than along other lines of endeavor. But if I read the signs aright it is an ubiquitous phenomenon. Metraux,[12] a cultural anthropologist, has noted that we keep a two-generation family in America, in which the younger ones are always moving out. Adulthood for all is dependent on independence. This creates a problem of what to do with older persons who, if they remain with children, are deprived to a certain extent of adulthood, or the children are deprived.

The frequency with which our patients are said to be suffering from chronic brain syndrome these days leads me to wonder whether this rather elegant phrase isn't serving something besides diagnosis. House officers seem to be fond of it. It sounds so final. It has an effect akin to that of a cliché; it delivers little or no information. Chronic brain syndrome when combined with a diagnosis of cerebral arteriosclerosis represents senile dementia in modern dress. The indications usually are that an irrevoc-

able mental state has set in, the implication being that certain changes have taken place in the brain due to arteriosclerosis. When I was a house officer and an apprentice we did not seem quite so sure. Our language included such terms as senile dementia and mental disorder associated with cerebral arteriosclerosis; we had a choice, if between Scylla and Charybdis. But we seemed to pause to wonder what we were about and to wonder what manner of disorder was this, where the brain may or may not show much the matter with it pathologically. I am an advocate of such pauses, moments of cool but imaginative wonderment about the meaning of disease and its relationship to things met by a body on its way to grace.

In these hurried days there is hardly time for pause and synthesis of thought. It is significant that the latest term for constructive thinking seems to be "brainstorming." Pascal's warning, which has done duty now these 300 years, though out of style still pertains, that most of the evils of life arise from a man's being unable to sit still in a room. When leisure goes out of the lives of men in the learned professions, we are in danger of losing our culture.

I should like to sketch besides my wonderment about the mental problems that occur in aging people some of the evidence about causation. I think it likely that I can do this best by describing in a sequence of sorts the way I learned about these disorders.

As a young neuropsychiatric house officer I had the usual introduction to the problem by taking care of many patients in a general hospital with what was then termed senile dementia. In the early 1930's, as today, these people were given the minimum of our time and were as rapidly as possible shunted to state hospitals and sanatoria for boarding the rest of their lives. As I try to recapture our thinking about these patients, we were as much embarrassed by them as any other feeling we may have had, a condition made tolerable for us by reason of the fact that they were soon to be gone. This state of affairs isn't much changed today; witness the frequency with which we move patients with chronic disorders out of the stream of medical consciousness, usually to somewhere in the suburbs or even more distant.

It was only later that I became aware of some of the social and economic factors that brought many of these patients to us. The loosening of family ties will all that it implies, the relaxation of discipline with its depreciation of elders, the critical financial decade and the accompanying unemployment beginning in 1929, the urban shift of population, conscription, even the isolationism rampant after the first world war; these and many other factors played a part. However, a busy young physician earning clinical spurs had little time in those days for such concepts; it was only later that they entered my thinking about senile dementia.

The next phase might be termed the neuropathological, when for a decade or so I became responsible for the study of the nervous systems of patients dying in a large general hospital. In other words, my avocation became neuropathology. I have written elsewhere about some of this experience and have remarked on the infrequency with which the circle of Willis is free of atherosclerosis in the brains of the persons over 50 years of age dying in a general hospital. Indeed, if rate of occurrence determined normality, then cerebral atherosclerosis—like pyorrhea—would be "normal." The distribution of atherosclerosis through the vessels of the brain need not concern us here except for mention of the predilection for the circle of Willis and to note the relative intensity of the process in the upper brain stem. A good deal has been learned [12] about changes in the parenchyma of the aging brain which I need not go into now. As a person grows old so do brain and blood vessels; yet neither senile dementia nor disease of blood vessels is a constant in aged subjects.[13] As a neuropathologist it seemed to me that the latter could not be the sole cause of the former.

The next phase in the development of my concept of senility, if one can partition learning in this way, came with intimate association with several nonagenarians who had economic security. One was the Pro-

fessor Emeritus of Neurology at my university, who died in 1956, at the age of 104. These people had outlived their contemporaries and welcomed friends from among younger generations. They were especially admired by children. Their reading was continuing; their knowledge of current events was comparable to my own. They were oriented toward the future. Somewhat isolated by problems of hearing and by reduced movement, they were not house-bound, though the most of their social intercourse took place in their own homes, which they maintained with the help of servants. As I had already reasoned but now saw clearly demonstrate, there was considerably more to senile dementia than an aging brain.

It was during these stages in my thinking that I developed a concept of isolation as a primary cause of senile dementia, a concept which I considered to be my own, since nobody had helped me to it besides the aged themselves. This possessiveness on my part, while naïve, was not unhealthy. As I was learning, the culture, to say nothing of the process of life itself, tended toward isolation of the aging person, but I didn't realize then as I do now the tremendous profundity of it. I had seen the isolation of the aged by the mores and by the loss of relatives and peers and by the loss of status as the employable age was steadily constricted and discipline was loosened by two world wars, to say nothing of the tissue changes which usually accompany aging.

Thomson's Lumleian Lectures, delivered to the Royal College of Physicians in 1949,[15] have reenforced my thinking about the senile psychoses. Professor of Therapeutics at the University of Birmingham, Thomson concerned himself with the problems of aging in the Midlands, where he studied a large population in institutions for the chronically ill. He could not dispel the uneasy suspicion that much of the psychiatric disorder in these institutions was the result of apathy and routine. He noted the development of positions of extreme flexion in bed which favored contractures, and the astonishing amount of food consumed by the senile person. Both the flexed (fetal) position and these feeding characteristics are signs of mental regression and withdrawal. Only some 25% of urinary incontinence could be charged to abnormalities of the genitourinary apparatus or its innervation; much of it patently was an expression of emotion. It could not be an expression of age alone, since there was little difference in the incidence in the 10-year groups 60 to 69, 70 to 79, and over 80. The soiling, dishevelled dress, and sexual exhibitionism quite common in senility are also universal manifestations of the early phases of human existence. Thomson described the profound apathy in chronic wards where patients seldom spoke and rarely moved. Although newspapers and a library service were provided, it was the exception of see a patient reading.

Apathy prevailed also in the large rooms for those who were able to dress and move about; there patients sat listlessly in silence. In the dining hall the patients maintained strict segregation of the sexes. Even the married couples did not sit together, and they rarely expressed any wish to do so. This prevailing calm was sometimes broken by outbursts of petulant misbehavior, which were commonly the result of childish jealousy, resentment, or misdemeanor.

Overt anxiety was manifested for only a short time after their admission from their homes, while they were still hopeful of recovery sufficient to allow them to gather up the threads of their customary way of life. There then began the subtle disintegration of human personality that is so common in these patients; in the chronic wards there was only apathetic indifference or frank psychosis. Thomson transmits the conviction that much of the mental difficulty that he witnessed in the aged is preventable.

I want to pass on to some recent neurophysiological and psychophysiological studies which may assist our thinking about mental states in the aged. The vast sensory input deserves more attention than it has had in our considerations of human isolation. Herrick[6] termed the sense organs the windows

of the mind and said that ". . . there is nothing in our experience, there are no mental powers, no skill in ratiocination or logical analysis, no capacity to forecast future events, no flights of imaginative fancy, which do not depend directly or indirectly upon sensory data. The mind of man is truly creative in the sense that new and hitherto unimagined ideas are fabricated, for the elements of experience can be recombined in new patterns. But the inventiveness of genius, whether dealing with material contrivances or with the less tangible whimsies of art and phantasy, can operate only with stuffs provided, in last analysis, through sense experience. We surpass the brutes in our capacity to use the data so provided and to supplement our limited and in some cases defective sense organs by artificial aids, such as spectacles and microscopes, but never can our thinking transcend the realm of sense experience. The most abstruse metaphysical speculation, in common with the highest flight of poetic fancy and the keenest esthetic appreciation, are earth-bound within the limits set by our physical sensory equipment.

"The widening of experience by artificial aids to the senses, by travel and by discipline of the powers of observation, attention, reasoning and appreciation makes for fuller and richer life. This is education."

Besides the known anatomical paths subserving sensation, Magoun [11] and his coworkers have described an ascending reticular system which appears to be a series of ascending relays distributed through the central core of most of the brain stem and thalamus to the internal capsule. Stimulation of this system yields arousal effects as determined by behavioral alertness and by electrical recording from the cerebral cortex. If this pathway is interrupted, the organism is as though asleep or anesthetized and the electrical record from the cortex becomes analogous to that of sleep. Jasper, Ajmone-Marsan, and Stoll [9] and also Adey, Segundo, and Livingston [1] have shown that stimulation of the cerebral cortex can influence the activity of this reticular brainstem system. Sharpless and Jasper [14] have demonstrated that the cerebral cortex of cats fails to respond with arousal to the repetition of a specific sensory stimulus after 20 to 30 trials. This ascending reticular system is responsive to stimuli from the environment and from the cerebral cortex. But habituation of the arousal reaction may be produced by repetition.

The clinical inferences from these neurophysiological studies are limited only by one's imagination, and one must guard against associations running wild. Linn's [10] study of behavioral disturbance following cataract extraction bears. It is rather widely known how readily patients may become psychotic whose cataracts have been extracted and who must lie quietly with both eyes bandaged. Then it usually requires no more than reassurance to terminate the abnormal behavior. A word or two and perhaps a touch of the hand appears to brush aside the psychotic episode. When the eyes are unbandaged and another sensory channel opened, psychotic episodes occur much less frequently and these primarily at night when alerting external stimuli are diminished. Here is evidence if it were needed that sensory input plays a considerable role in mental function, indeed it seems to be pretty close to the stuff of sanity.

This leads rather naturally to the work of Hebb and others [4,5] on sensory isolation. The production of unrealistic thinking in healthy young subjects by blocking sensory avenues at the periphery has gained rather wide recognition and does not require more than mention here. With prolonged exposure to a monotonous environment thinking is impaired, emotional responses are altered, visual function disturbed, hallucinations occur, and the electroencephalographic pattern changes. So it appears that sensory stimuli have the potentiality of maintaining arousal and alertness but that they lose the power of doing so if they are repeated monotonously in an unchanging environment. Under these circumstances the activity of the brain changes and abnormal behavior is the result. We can now better

understand Christopher Burney, who wrote after four years of solitary confinement, "Variety is not the spice of life; it is the very stuff of it."

Before trying to draw these threads together, it may be well to examine some of the work in progress on the blood supply of the brain. The cerebral circulation must be thought about in any consideration of chronic brain syndrome predicated on cerebral arteriosclerosis. Some authorities would blame dementia of the aged mainly if not entirely on inadequate cerebral blood supply.

We are not entirely clear about the physiopathology of strokes. Cerebral infarctions are not always associated with occlusion of the vessel directly supplying the infarcted area. Some of us had made a rather heavy investment in the concept of cerebral vasospasm, analogizing from the transient cortical phenomena that occur frequently in migraine. A prolonged state of vasospasm occurs in the vessels on the brain surface after experimental cerebral embolism with solid materials. But our data were incomplete; though we had examined many brains and circles of Willis, that terra incognita of neurology, the neck had been untouched. (Cervical hyperostosis was long in gaining recognition.) This was so because pathologists doing autopsies in this country were restrained from entering the neck either by ennui or what is more likely by the interdiction of morticians. So we remained in the dark as to what was occurring between the heart and the circle of Willis.

There is now at hand increasing evidence that the internal carotid and the vertebral arteries are the frequent sites of atheromatous stenosis and thrombotic occlusion. That portion of the brain most distant from the source of supply—the heart—suffers when the cerebral circulation is failing.[8,17] This most distal area is not so readily determined, even with adequate survey of both internal carotid arteries and both vertebral arteries, since we have to know also about the nature and state of anastomoses thrown into function by a compromised cerebral blood flow, to say nothing of the structure and function of the circle of Willis.

As long ago as 1874, Heubner[7] described anastomoses between all orders of the meningeal arterial system, varying in number and size and position from one case to another. The evidence is that in health these meningeal anastomoses are not functional since the pressure on both sides of them is an equipoise. When an occlusion of one or another part of the cerebrovascular tree prejudices the cerebral circulation, pressure on the two sides of an anastomosis becomes unbalanced and blood flows through it, and adequate circulation may be maintained to an area which otherwise might be deprived. It seems that the function of collateral circulation in the brain is even more complex than that of the usual cerebral circulation; collateral circulation is not as steady or as stable. While the mechanism is not thoroughly understood, failure of collateral circulation appears to depend mainly on its caliber and patency and the continuing effectiveness of the heart and general circulation.

In certain people aging interferes with the sensory avenues, surely contributing to their isolation. Sight is dimmed; hearing and proprioception are reduced by methods imperfectly understood. The selection of sight and sound particularly should be one of those incongruities that cause us to pause and wonder and to commit that intense moment of cool but imaginative attention; these effects have not been elucidated by neuropathology. Perhaps this selectivity may have some meaning as conservation of energy at a time of life when energy expenditure is at a premium, those sensations being excluded which project the greatest distance away. It may represent a kind of drawing in of antennae, egocentrically. It isn't uncommon that blurry-eyed and deafened aged folk seem sometimes to see and hear things that they are not meant to. Or they may fight against the use of hearing or visual aids. With aging, sexual stimuli become of a low order of intensity, a con-

tribution toward isolation. On the motor side, diminishing flexibility tends to discourage movement and the search for sights and sounds, and we now have some scientific conception of the penalty inherent in monotonous sensory input.

In the brain stem interference with the ascending reticular system by whatever means results in akinesis and diminished alertness. At the highest level, the cortex appears to have the capacity of damping down alerting mechanisms and otherwise controlling the acuity of input and accuracy of output; it may "exclude" stimuli.

It is conceivable that lesions of parenchyma or of cerebral circulation strategically placed may result in some of this dysfunction. However, there is on one hand the paradox of severe histological change with no deficit in function and on the other of minimal histological change with extreme deficits in mental function. Nor can electroencephalographic changes in the aged be correlated with psychic functioning. These and other incongruities should again give us pause to wonder about the nature of the process.

The monistic approach to a problem so complex as senility is bound to be fallacious; indeed, it should have gone out of style. Among causes, we have to consider the predisposing, the precipitating, and the perpetuating, to list categories. Even if the pluralistic approach were illogical, I should be inclined to argue for it, since it contains the seeds of hope—hope for therapy and hope for prevention. "Hope is itself a species of happiness," said Samuel Johnson, "and perhaps the chief happiness which this world affords." Hope is the element that has been most missing from the affairs of the aged.

The climate that surrounds oldsters would form a chapter in itself, a chapter that I am not prepared to write. A lively responsibility previously sheltered many an oldster within the family confines who may now be found on the doorsteps of our hospitals, asylums, and nursing homes. An attitude that looks constantly to the State to take on responsibilities that should belong mostly to the family is devitalizing; it is in the healthiest societies that the ill and the weak and aging are cared for in a personal manner. Detailing the ways in which an aging person is encouraged and assisted toward isolation could occupy us the rest of the evening. The retreat offered by the human mind—an organ so wonderful that it can afford an escape from a situation while remaining in it—may be a way of dealing with such attitudes.

In treating the mental disorders of the aging we have as yet no method for improving brain blood supply or of reversing parenchymal cellular change. Until we develop these tools, and subsequently for that matter, the human relationship in treatment is of primary importance. There needs to be an optimistic, straightforward, and steadfast approach to the patient by physician of whomever, free from fear and embarrassment. The person doing the treating must be aware of the dynamics of the problem. He has got to know about the people who have been important throughout the patient's life and be interested in events as they happened to him in a longitudinal fashion. Knowing the meaning of the symptoms to the patient allows a chance at their modification and, if not change, then acceptance. The patient must be convinced of the doctor's personal interest. The simplest way to do this is to be interested, and the effort will have its reward. His interest is more potent than knowledge and skill, the latest development in science, or the utmost virtuosity in art. In no case must there be the usual resignation to further deterioration.

We must try for certain modifications of the environment of the aged. Thomson [15] has outlined this gnawing at the conscience of society as follows: "In the interest of social cohesion psychology and anthropology favour the second course [encouraging friends and families to care for their aging whenever possible rather than expecting the State to do so], and so does ethics, and, while it has been the constant aim of religion and morals to extend the affections of the individual beyond the range of his personal

and group relations, both agree that such extension must be based on a lively sense of responsibility for the weaker members of the family and on service to them. Aesthetics in days of realism is often confused with sentiment, but there is a beauty and a value in personal service to a crippled friend or relative that no hospital can rival. Claims of expediency and economy may be vulgar, but they are insistent, and the fact that care of the sick and disabled in their homes is cheaper than in institutions is worth emphasis.

"For all these reasons, and to avert the distressing disintegration of human personality that is so common in patients who lie for years in an infirmary, it would be wiser to endeavour to preserve the sense of family responsibility and to encourage people to tend their own sick and guard the aged.

"That does not mean that families should be expected to bear the whole burden. Society must help them, and the problem really hinges on the type and extent of assistance to be provided. Institutions will always be necessary, but the aim should be to reduce the demand for them, and the measures to be adopted must not conflict with the claims of human instinct or with the principles of ethics, morals, and religion."

We come now to prevention, which probably should not be separated from treatment. Whitehead remarked about a thesis that it need not necessarily be true if it is interesting and exciting. I find thinking about prevention the most interesting and exciting prospect of the problem of senility. It deserves attention and experiment, an experiment which today perhaps can only be set up in each of us by ourselves. It is likely, considering the evidence that I have put before you, that we can dedicate ourselves to the business of avoiding senility? As a house officer—knowing less—I would have thought such an idea unlikely; today—knowing more—I am not so sure. Here I find a place for a method of my favorite medical philosopher, Wilfred Trotter,[16] who said: "The only way to the serene sanity which is the scientific mind—but how difficult consistently to follow—is to give to every fresh idea its one intense moment of cool but imaginative attention before venturing to mark it for rejection or suspense, as alas nine times out of ten we must do."

It seems to me that if it be true that sensory avenues require a certain traffic, we can learn what that traffic should be. Surely we can search for and admit nonmonotonous sights and sounds, in other words, new stimuli, and partake in activities that are apt to keep us growing. In other words, we can continue to be students, which is in accord with Goethe's thought that: "All that is human must retrograde if it does not advance."

Thoreau said that "the perception of beauty is a moral test." It may be that such percepts have more than moral connotation; indeed we begin to wonder if they may not be a way of life. I can see nothing wrong with the concept that we constantly prepare ourselves for living or for dying, if you will. We know that persons with senile psychosis have certain personality traits; they are rigid and sensitive in that they misinterpret communication. In their past they have tended to restrict their interests to narrow sectors, and their emotional investments have occurred in areas which have little or no future. They lived too much for the present, and later they connect the past instead of the future with the present. We all know people who behave in this manner long before they reach old age, but they are not displaced or isolated—at least not immediately—not only by reason of their relative youth but because they are considered productive. Such younger persons live to work, action absorbing their anxiety. But when such activity is no longer possible, then what? These people have had no time for esthetic development and of the search for sights and sounds. Indeed, usually they are derisive of them.

I like to cite Daniel Drake (1785-1852),[8] the founder of modern medicine in Cincinnati, not only because I believe him to be one of the most significant men of medicine but because he said so much so long ago that

bears on the problems that continue to beset us. He noted that diligence in youth may be preventive medicine. In the lovely letters that he wrote to his children concerning his own early years is the following passage: "If a provident temper of mind make you desirous of guarding against the gloomy insignificant—the sad and solitary nothingless of an ignorant old age, you must accomplish it by industry in youth; industry is peculiarly appropriate to this object since, in our declining years, the knowledge acquired in early life is almost all that remains with us; the first inscriptions on the tablet of the mind are the last to be effaced. What a resistless motive for early diligence is suggested by this important law of human nature; and from its frequent violation, how few like Nestor in the Iliad, become in old age the living oracles of wisdom to the rising generation."

Surely we should give cool but imaginative attention—in the sense of Trotter—to the possibility that senility is a learned pattern. Sir James Crichton-Browne, the English psychiatrist, who remained alert throughout his 97 years, said: "There is no short cut to longevity; to achieve it is the work of a lifetime."

I have forgotten the source of the following passage which bears on the final point that I wish to make. "Diseases are natural phenomena amenable to study by the techniques of science. It is obvious, also, that because human nature is so complex—both physically and mentally—it can be influenced by countless ill-defined manipulations for which experience and intuition are more effective than scientific knowledge." Here then an example of William Wordsworth's experience and intuition; I don't mind citing genius in an inquiry such as this because I too have the feeling that genius somehow "knows." In his poem "Expostulation and Reply," which is dated 1798, we find

> "The eye—it canot choose but see;
> We cannot bid the ear be still;
> Our bodies feel, where'er they be,
> Against or with our will.
> Nor less I deem that there are Powers
> Which of themselves our minds impress;
> That we can feel this mind of our's
> In a wise passiveness."

Wordsworth spoke in the flush of youth; even his eye and ear did not function quite as well later in life. But they functioned well enough. The secret—as he tells it—to his receptiveness is contained in those wonderful words from the unconscious of genius, "a wise passiveness," words pregnant with meaning, so poignant, so global that I can't believe that the young Wordsworth consciously recognized the potentiality of his own creation. "It is a wise father that knows his own child." It seems to me that "a wise passiveness" is akin to the philosopher's "know thyself," and to Schiller's admonition to those who would compose to "Remove the watchers from the gates of intelligence," and to Coleridge's marvelous definition, "The streamy nature of association, which thinking curbs and rudders."

How to do these things that genius does naturally, how to develop "a wise passiveness" still remains beyond defining, and to continue it into old age, even more of a mystery. By the examples of a host of people, such as Plato, Michelangelo, Goethe, Franklin, Adams, Jefferson, Verdi, and Oliver Wendell Holmes, we know that it has been done. My feeling today two milennia after Plato, also is not to squander this legacy from these elders—however we know it—lest we find ourselves paupers during "the last of life, for which the first was made."

Department of Neurology, Cincinnati General Hospital (29).

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Twixt the Cup and the Lip

HARRY F. DOWLING, M.D., Chicago

Drugs are discovered, manufactured, and tested by scientific methods. On the other hand they are produced and marketed through a blend of personal and social motives; they are prescribed by doctors with varying knowledges and skills, and they are taken by patients who have different degrees of information, interest, and precision. Drugs are brewed in the cup of science; they are drunk through a patient's lips, and "there's many a slip twixt the cup and the lip."

Scientific attention is usually turned toward the discovery of drugs; in the present paper I shall consider the path from their development to their use. As an example, let us take chlortetracycline, one of the first antibiotics to be produced by a pharmaceutical company. After screening hundreds of specimens of soil, Duggar isolated Streptomyces aureofaciens, in the fall of 1945. Its in vitro antibacterial activity was demonstrated later in the same year.

Preparation of crude concentrates that protected animals against bacterial infections required an entire year, and further purification and initiation of large-scale production required nearly two years more. It was not until September, 1948, that clinical tests were considered adequate for submission of the data to the Food and Drug Administration. Approval by this agency was granted in October, 1948, and chlortetracycline was finally marketed on Dec. 1, 1948.[1]

The path of a drug from cup to lip, which took over three years in the case of chlortetracycline, is shown in Figure 1. Basic research by medical schools, pharmaceutical companies, and others leads to the discovery of a new drug. It is produced in a form suitable for administration by the pharmaceutical manufacturer. Its efficacy must then be tested in vitro, and its efficacy and toxicity, in lower animals. If these tests are satisfactory, the drug is tried in patients by investigators outside of the pharmaceutical industry. The accumulated information is then submitted to the Food and Drug Administration for approval or to the National Institutes of Health in the case of biological products. When approval is forthcoming the drug can be packaged, advertised to the profession, and sold. At the same time, investigators who have tried the drug in patients are informing the medical profession when and how this drug should be used. All of these paths lead a single goal: administration to patients. This benefits the patient through the prevention, amelioration, or cure of disease and brings profits to the pharmaceutical industry and related groups. These twin benefits act as sources of energy to start the process over again.

This system is an outstanding example of man's genius for organization. It has been developed by idealistic motivation, along with down-to-earth planning; it balances the interests of scientist, investor, producer, physician, and patient. And it has filled the cup to overflowing. The number of effective drugs is beyond the highest hopes of a century ago and is increasing all the time. In the thirty-year period from

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From the Research and Educational Hospitals and the Department of Medicine, University of Illinois.

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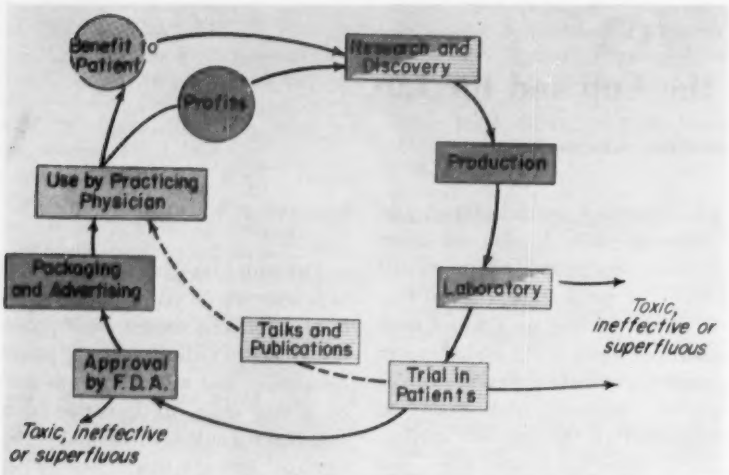
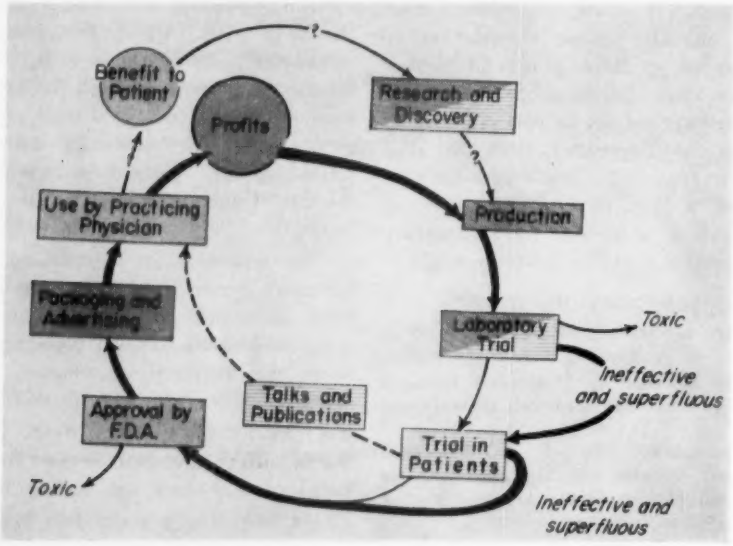


Fig. 1.—Diagonal lines refer to the pharmaceutical industry; horizontal lines, to the investigators in medical schools and hospitals, and stippled areas to other groups (government agencies, the practicing physician, and the patient).

1905 to 1935 new drugs were introduced into the United States "Pharmacopeia" at a rate that averaged six per year, while in the succeeding twenty years the average yearly rate was thirty-seven.[2]

Yet the system, like all systems, can be perverted. The process of fundamental research, followed by the development of worth-while new products and the successive stages necessary to bring them to the patient, is a long one. The desire to help the patient and the desire for profits provide sufficient energy to power the process; but some have discovered that if this energy is applied at a later stage, the path from profit back to profit again can be speeded

Fig. 2.—See Figure 1 for key.



up. This is shown in Figure 2. Energy, instead of being directed toward research and the discovery of new drugs, is frittered away on dozens of unimportant modifications designed to compete with drugs that are already available. One example of this is the marketing of mixtures of antibiotics. As of November, 1956, there were on the market twenty-nine preparations containing two antibiotics, twenty containing three, eight containing four, and four preparations that contained five antibiotics apiece.[3] I have shown elsewhere[4] that there is no good reason for the use of any of these sixty-one mixtures.

If this trend continues, we shall soon reach the chaos that exists in Germany. According to a recent article in *The Lancet*,[5] there are about 6000 proprietary preparations marketed in Western Germany, made by 565 different firms. Most of these preparations contain several or many substances; five or six is the rule, and more than ten is not at all rare. One firm has put twenty-two different substances into one tablet. It has become unfashionable to use one drug by itself. When the author of the article asked for ephedrine tablets in a big hospital, he was told that these were no longer stocked.

This side-tracking of energy within the system has further effects. When the drugs that are produced so prodigally are tested in the laboratory, only those are eliminated that are obviously toxic. Drugs that are superfluous because they duplicate the action of others that are already available and drugs that are of dubious effectiveness are continued in the process and eventually reach the market (Fig. 2). For instance, thirty-three different antihistaminic drugs are being sold at present,[6] all having practically identical actions but different names and dosages. Similar excesses can be found among other groups of drugs, especially the vitamins, the antispasmodics, and the tranquilizing drugs.

At the next step in the process pressure is applied upon investigators to report that all the drugs recently produced are beneficial to patients, that they are better than existing drugs, and that they have fewer side-effects. Since this tremendous multiplication of new drugs exhausts the existing facilities for clinical investigation, inexperienced investigators are cajoled into assessing drugs in patients. Some learn the proper methods and acquire a critical sense during the experience; most do not but unwittingly call a spade a diamond—to the confusion of the Food and Drug Administration, the exasperation of the experienced and honest investigators, the quick profit of that particular manufacturer, and the loss of prestige of the medical profession and of the pharmaceutical industry as a whole.

Increased pressure is applied in turn upon the Food and Drug Administration. No words can speak too highly of the services rendered to physicians and patient alike by this dedicated body of public servants. Quietly and unobtrusively, patiently and honestly, they attempt to judge the merits of a drug solely on the evidence presented to them. Their problems, however, are similar to those of every regulatory agency of the government: they hear one side of the story loudly and incessantly; they hear the other side only sporadically and feebly. It is the drug manufacturer's business to present his viewpoint; it is to his interest to present it attractively and forcibly. The consumers, on the other hand, have no paid advocates. Their viewpoint is presented by persons who must spare time from everything else to do it and who are not usually well acquainted with these channels of communication. This is all the more reason why, in the field of the regulation of drugs, physicians and organizations of physicians, such as the American Medical Association, should make it their business to advise the Food and Drug Administration.

The excess pressure is applied next to advertising. The description of the drug on the label and the circular accompanying the package must be accurate and well documented and must be approved by the Food

and Drug Administration. Advertising pertaining to a drug, on the other hand, is under the jurisdiction of the Federal Trade Commission, who can stop a company from making a particular statement only if the statement constitutes an unfair or deceptive act. This opens the way for abuses.

Within recent years the drug industry has discovered that the techniques that had been used so successfully in the advertising of soaps and tooth pastes and of cigarettes, automobiles, and whiskey could be used as successfully to advertise drugs to doctors. Advertising to doctors has become flamboyant, as shown by two-page gaily colored spreads in nearly every medical journal. Advertising has become incessant; nearly identical advertisements for a new drug appear in each day's mail for weeks on end. Advertising is without question confusing. The multiplicity of trade names makes it difficult to remember the actions and uses of any. Richardson Evans, writing in the English *National Review* in 1890, said: "Suppose a dozen people are in a small room. Two begin to talk to each other at the top of their voices. The others must either give up conversation or shout also. The result is that no one hears as well as before and that comfort is at an end. So it is with advertising. . . ."[7] Advertising to doctors has now reached this peak, and we are deafened by the din.

This leads us to the next step in the process: the use of drugs by the practicing physician. The doctor's sources of information include textbooks, journals, and speeches, written or delivered by those who have studied the drugs in laboratories and in patients. Most practicing physicians do not see a sufficient number of patients with any one disease to make a critical trial of a new drug themselves. When the drug becomes available the most they can do is to acquire skill in its use. If this information is "beamed" clear and true to the doctor, he is willing to listen to the "commercials" and patronize those who have, through their investments and their foresight, brought the drugs to him. But today the "commercials" are so loud, incessant, and brash that they jam the channels of communication. The bewildered physician prescribes by suggestion and not from information.

At this point the reader will say: "Well, even if this makes the physician a shifting weathervane and the patient an unwitting guinea pig, the writer must be an ingenuous idealist to expect the pharmaceutical manufacturers to change their methods so long as they are putting money in their pockets." This last phrase is the key to the answer. You will recall that the twin sources of energy for the system are profits and benefit to the patient. It is already evident to most doctors, and it will soon become evident to the public, that energy has been diverted from the pathway that leads to the greatest benefit to patients. With the inevitable disillusionment that comes with the failure of each useless modification to make any advance, the pharmaceutical industry will lose its prestige and with this will lose its financial backing. It will fall, and the medical profession will be dragged down with it. Since such a catastrophe would involve doctor, industry, and patient alike, we may well look to see what each can do about it.

To physicians I would say first: Keep informed. Learn the mechanisms by which drugs work, rather than the results somebody says they produce. Look for and remember the generic name, for this tells something about the drug, while the trade name tells nothing. Avoid substituting drugs for diagnoses.

Furthermore, since advertisements for new drugs appear so quickly, some mechanism must be set up to bring authoritative information rapidly from investigator to practicing physician. The challenge is thrown to medical societies, medical schools, and specialty groups: keep the profession informed!

My second suggestion to physicians is, inform the public. As Vannevar Bush has

said[8]: ". . . public opinion is not formed by the radio and the press or even by those who control these media. It is formed by that minute fraction of the population which thinks and speaks, by that small but powerful minority, disagreeing on every issue, arguing and ridiculing, which looks beyond the diversion of the moment and influences because it labors to understand." With regard to drugs we are that "small but powerful minority," and we must use every means to make our opinion known. When a doctor prescribes a drug for no reason except that the patient wants that drug, the doctor is allowing the lay press to take over the job of health educator to his patients. The good physician explains instead of prescribing.

My third suggestion to doctors is to reject misleading information and repudiate those who purvey it. Doctors should read advertisements critically. They should write to editors of journals and to drug manufacturers when they question the truth of an advertisement. They should not listen again to someone who has misled them once. They should prescribe as far as possible only those drugs made by companies with high standards of advertising and read only the journals that accept that kind of advertising.

In the past the Council on Pharmacy and Chemistry of the American Medical Association (now the Council on Drugs) has led the fight against false advertising by quacks and vendors of patent medicines. The battle front of today has shifted, and false advertising to the public is no longer the major issue. For the future the Council needs to align its forces against false advertising to the doctor.

To pharmaceutical manufacturers, I would make three suggestions: (1) that they emphasize basic research and the discovery of new drugs and avoid minor variations of existing drugs; (2) that they weigh the proposals of their sales departments in the light of advice from their scientific staffs and from competent impartial clinical investigators, and (3) that they revise their advertising methods. Advertising should not be premature; advertisements for a new drug should not appear before a single clinical article is published in a reputable medical journal. Advertisements should be in keeping with the dignity of the industry from which they come and the good sense of the profession to which they go. The time is already past due for reputable manufacturers to establish a code of ethics for advertising and abide by it. When this has been done the words "ethical manufacturer" will mean a manufacturer who works for the good of the public rather than meaning, as at present, one who advertises only to the medical profession, no matter how he advertises.

The regulatory agencies of the government function as impartial judges for the benefit of the consumer. Laws always lag behind actuality, and budgets are always deficient; but in spite of these limitations the regulatory agencies deserve great credit for keeping the present system from getting out of hand altogether. How can they do the job better? Certainly they should insist upon honest and thorough investigations by clinical investigators. They should inquire how the cases were obtained for trial; were they selected out of a larger number of cases and, if so, by what criteria? Funds should be available to them for financing tests of drugs when the evidence submitted it equivocal or unconvincing. They should also be able to employ consultants to advise them in difficult cases. These agencies need the strong backing of the medical profession; the patient's welfare must be kept continually before them so as to counteract the obvious pressures from the pharmaceutical industry.

Many people believe that the laws should be amended so that the Food and Drug Administration can pass on the efficacy of a drug. At present, except in the case of the drugs that are certified, which include insulin and certain antibiotics, the Food and Drug Administration cannot prohibit the sale of an ineffective drug; its only recourse

is to seize the drug as misbranded if a therapeutic effect is claimed in the circular that accompanies the package. This seems a roundabout way to protect the public.

Furthermore, the present laws leave all advertising, except that which accompanies the package, to a separate agency, the Federal Trade Commission. In spite of the excellent cooperation that exists between the two agencies, this is a cumbersome method which has not succeeded in giving adequate protection to the patient. Many people believe that the law could be enforced more efficiently and more completely if advertising as well as labeling were regulated by the Food and Drug Administration.

My suggestions can be summarized in two words: information and regulation; prompt and exact information for the practicing physician from the investigator, the professional societies, the medical journals and the specialty groups; willingness on the part of capable investigators, teachers, and other leaders in medicine to spend time in spreading the truth about drugs; probity and sanity on the part of the manufacturers in keeping advertising factual rather than suggestive, direct rather than irrelevant, truthful rather than misleading; recognition on the part of the practicing physician that his is the final responsibility for the use of a drug and that he cannot give this decision over to anyone else. Regulation there must be for those who will not work from higher motives: regulation by industry to the extent that it can be done; regulation by organizations of physicians where they can help, and regulation by government where the others fail to do the work. Let those who object to the third alternative strengthen the first two.

These things should be done; these things can be done; shall we here agree that these things will be done? In the words of George Washington, "Let us raise a standard to which the wise and just can repair."

Research and Educational Hospitals, University of Illinois, 840 S. Wood St. (12).

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The Nonrheumatoid Connective Tissue Disorders

JOHN H. TALBOTT, M.D., Buffalo

Diseases associated with a disturbance of connective tissue have been recognized for centuries, but the broad concept of these maladies is contemporary. Rheumatoid arthritis and acute rheumatic fever are identified readily as the commoner connective tissue disorders. The less common disturbances include systemic lupus erythematosus, polyarteritis, systemic scleroderma, acute dermatomyositis, and thrombotic thrombocytopenic purpura. There are selected physicians who accept yet a broader definition and include such maladies as acute glomerulonephritis, chronic nonspecific ulcerative colitis, sarcoidosis, idiopathic thrombocytopenic purpura, and malignant hypertension.

Conclusive proof for or against the inclusion of these latter conditions in the connective tissue group is lacking. One of the strongest arguments for inclusion is the clinical response to steroids, similar to that in the accepted connective tissue category. I do not accept this evidence as convincing, however, and believe that we should limit our concept rather than broaden it. In this presentation, therefore, I have considered it appropriate to confine the discussion to systemic lupus, scleroderma, dermatomyositis, and polyarteritis, with casual references to the two common rheumatic disorders.

Although the term connective tissue disorder, used in the title, identifies the subject for discussion, collagen disease might suffice and to some would be equally acceptable. Much of the mysterious aura formerly associated with the term collagen disease has been dispelled as a result of familiarity. The substance, connective tissue, is understood by everyone. Collagen is but one chemical and morphological feature of connective tissue. This term was used in the current sense hardly more than a decade ago by Klemperer, Pollack, and Baehr [1] after the accumulation by Baehr in New York of 23 cases of "A Diffuse Disease of the Peripheral Circulation Usually Associated with Lupus Erythematosus and Endocarditis." [2]

At the onset of symptoms in the less common maladies, clinical and laboratory findings may not be particularly helpful, and a healthy skepticism regarding a definitive diagnosis may be justified. Also, in the initial weeks, months, or even years of the clinical course of the less common maladies a presumptive diagnosis of acute or chronic rheumatoid arthritis or of acute rheumatic fever may be justified on the basis of the clinical findings. One should also include idiopathic epilepsy in this initial presumptive diagnostic category. The features that characterize each of the respective maladies may persist as evidence in support of one of the less common disseminated dyscrasias appears. Eventually the patients that fall in this particular category under discussion present the clinical and laboratory findings of systemic lupus, systemic scleroderma, or, less often, acute dermatomyositis or polyarteritis. We do not know from the current state of our knowledge concerning these connective tissue dyscrasias, whether the disease originally was, for instance, rheumatoid arthritis and subsequently

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From the Departments of Medicine, University of Buffalo School of Medicine and the Buffalo General Hospital.

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evolved into one of the less familiar maladies. An equally acceptable explanation is that the less familiar malady presented the more familiar joint symptoms incidentally and that one disease only was present throughout the course of clinical symptoms. I favor this latter explanation in most instances.

Rheumatoid arthritis remains the connective-tissue disease most frequently encountered in clinical medicine, irrespective of the branch or specialty of medicine pursued. Until recently the diagnosis of rheumatoid arthritis in the earlier years of the natural history of the malady was based upon clinical findings only, and no conclusive laboratory tests or procedures were available to confirm the clinical presumption prior to the development of chronic deforming changes in the joints. With improved techniques in the handling of sheep cells or latex particles there is available for the first time a satisfactory laboratory test to confirm our clinical impressions. Just what the agglutination procedures eventually will reveal in regard to the identification of the arthralgias that may accompany the less familiar collagen disorders remains to be revealed. More and more evidence is accumulating to suggest that these agglutination procedures are specific for rheumatoid arthritis and usually will be negative in a case of systemic lupus with joint findings that suggest rheumatoid arthritis.

This poses the question as to what constitutes atypical rheumatoid arthritis. Some patients with typical rheumatoid arthritis subsequently present clinical and pathological evidence of systemic lupus erythematosus or one of the other diffuse connective tissue diseases. It is possible that the initial clinical symptoms should have been attributed to some other malady than typical rheumatoid arthritis if one of the disseminated diseases appears eventually. If the L. E.-cell phenomenon is demonstrated or positive findings on muscle biopsy are reported in a patient with clinical rheumatoid arthritis a knotty problem is at hand. It is my current belief that when a diagnosis of rheumatoid arthritis is made it should be assumed that it is the garden variety type, with neither L. E. cells in the peripheral blood nor positive findings on skin or muscle biopsy. On the other hand, when a sufficient number of L. E. cells is demonstrated or the findings on skin and muscle biopsy are positive for scleroderma or dermatomyositis, even though the patient has what appears to be clinically typically rheumatoid arthritis, I favor the diagnosis of the less common connective tissue disorder. Note well, however, that it is necessary to demonstrate a "sufficient number" of L. E. cells or that the findings on skin and muscle biopsy should be "positive" in order to qualify. These assumptions in reference to rheumatoid arthritis are probably applicable also to acute rheumatic fever. In our experience a differential diagnosis between acute rheumatic fever and systemic lupus is not entertained frequently because the incidence of acute rheumatic fever is considerably less than that of rheumatoid arthritis. There are, however, instances in which what appears superficially to be acute rheumatic fever proves eventually to be one of the other connective tissue dyscrasias. Following this dogmatic introduction, selected items pertaining to each of the less common maladies will be discussed.

Polyarteritis

Polyarteritis was identified formerly as periarteritis nodosa because of the aneurysmal dilatation or gross nodulations along the arteries, internal or peripheral, of the body. It is a disease predominantly of males. Neurological findings, particularly peripheral neuritis, are the rule, and the disease may not be suspected until the peripheral neuropathy or even renal insufficiency develops. A marked eosinophilia is present in a minority of instances only. The diagnosis should be confirmed by a skin or muscle biopsy, and, in the absence of localized muscle symptoms, either the deltoid or the gastrocnemius area may be sampled.

One of the variants of polyarteritis is the localized form, such as in the gallbladder or the uterus, in which dissemination presumably is delayed for one or more years. A similar phenomenon has also been reported in children.

Hypersensitivity is thought to be responsible for polyarteritis in some patients.[3] In fact, a history of bronchial asthma has been the initial clinical process in a few instances. This was emphasized almost 20 years ago by Rackemann and Greene.[4] When the acute vascular disease develops in patients with bronchial asthma, death occurs usually within a matter of a few weeks or months. Although hypersensitivity may be the determining factor in the pathogenesis of polyarthritis, the incidence of this dyscrasia has not increased to the same alarming extent as has systemic lupus erythematosus. With the increased employment in clinical medicine of a multitude of new organic compounds, the possibility of an increase in incidence of polyarteritis seems reasonable. This possibility has not become factual up to the present time.

The duration of the disease is quite variable. The clinical demonstration of peripheral neuritis or the development of hematuria has been ominous in our experience. On the other hand, we have observed some patients who have had a positive pathological diagnosis without diffuse peripheral neuritis or renal abnormalities and who have lived for several years with no more specific medication than the nonspecific steroids. This course is not to be confused with the isolated observation of the localized form in which the disease has been recognized pathologically in organs such as the gallbladder or the uterus and the patient has continued to enjoy good health without symptoms and without any recognized form of therapy.

Systemic Scleroderma

Systemic scleroderma, a disease characterized by withering of the skin, may begin with arthralgia or symptoms of Raynaud's syndrome, which suggests rheumatoid arthritis or acute rheumatic fever. The skin of the face and the hands, particularly, appears to bear the brunt of the insult. It is surprising to discover that the physician, patient, or relatives may overlook the development of scleroderma because of the extremely insidious and slow rate. One might assume that a person afflicted with scleroderma is merely a "wrinkled old lady," a victim of premature aging. In addition to atrophy and obliteration of normal linear markings of the skin, purpuric spots and telangiectasia may appear.

Examination of the hands may reveal swelling and obliteration of the normal markings in the acute phase of digital scleroderma; in the later stages, marked atrophy, a glistening skin, restriction of motion, or gangrene may be noted. Marked atrophy of the tufts may be demonstrated by x-ray. Although it may not seem necessary to seek pathological confirmation in the well-developed case of scleroderma, it is highly desirable in the early stages to have positive or negative pathological evidence. It would seem that a likely site for biopsy would be the skin and subcutaneous tissues of the affected digits. For cosmetic reasons, the digits have obvious disadvantages. Usually it is not practical to remove a sufficient amount of tissue for pathological examination from these parts. On the other hand, the deltoid is a fairly acceptable site, and even though the overlying skin may not appear to be involved, if the disease is present the morphological changes may be recognized.

Roentgenographic examination of the entire gastrointestinal tract may be revealing in systemic scleroderma as well as in acute dermatomyositis.[5] Marked atony of the esophagus and small bowel should be searched for, even though symptoms pointing to involvement of the gastrointestinal tract may be denied. The motility of the small bowel may be altered, and a pattern not unlike a deficiency state may be observed. The changes in the large bowel

may suggest ulcerative colitis, save for involvement of the sigmoid. Examination of the chest discloses interstitial fibrosis in a significant percentage of afflicted.

Diffuse calcinosis is a late complication of systemic scleroderma. The tips of the fingers, the extensor surfaces of the arms and the legs, the buttocks, the shoulders, and the face may be the site of calcium deposits. Extrusion of calcium masses from subcutaneous deposits in any of the areas enumerated may be observed. The tendency to formation of abscesses or the development of infection has never been a serious problem in our cases except for the association of gangrene and calcinosis in the terminal phalanges.

There is one variant of systemic scleroderma that I will mention briefly because we have observed three such patients who have died of this unexpected involvement in a period of less than one year. In two instances the presenting symptoms suggested rheumatoid arthritis, while in the third malignant hypertension seemed most likely. Death occurred within a few weeks or months from the time of onset of acute symptoms in each instance. The cause of death was uremia and renal insufficiency. Pathological changes considered to be characteristic of scleroderma were observed at postmortem examination.

Acute Dermatomyositis

Acute dermatomyositis is a diffuse musculocutaneous process that may be recognized usually as a distinct clinical entity from systemic scleroderma. The diagnosis may not be suspected until after a long siege of muscle or joint distress, with or without permanent joint symptoms, but with the mistaken diagnosis or atypical rheumatoid arthritis. In other instances swelling of the face, particularly of the periorbital region, as well as erythema of the malar prominences may suggest nephrosis, subacute glomerulonephritis, or systemic lupus erythematosus. Symptoms in dermatomyositis tend to be central, in contrast to scleroderma, which reveals peripheral involvement. In dermatomyositis the shoulder girdle may be affected particularly, and the patient is unable to elevate the arms above the head. Erythema may be present with or without subcutaneous edema. It may be mottled or diffuse, livid or rosy. The term heliotrope has been applied to the appearance of the affected eyelids. The face and the V of the neck are the common sites of erythema. These are followed in frequency by involvement of the extensor surfaces of the arms, the legs, and the trunk. Pigmentation, atrophy, and telangiectasia are cutaneous manifestations that develop later.

A majority of patients have muscle tenderness; others deny this symptom. The dissociation between subjective and objective evidence of muscle involvement has been noted. The consistency of involved muscles may appear normal, or they may feel doughy, firm, and fibrous. The patient may walk with an unsteady gait and a shuffle because of weakness of the skeletal muscles. Weakness of the facial and glossal muscles makes eating and speaking difficult.

The coexistence of neoplastic disease and dermatomyositis is noteworthy. Bezecny[6] has emphasized particularly the coexistence of the two conditions. The incidence of malignancy and dermatomyositis has been reported in the literature to be as high as 18%.[7] The following lesions have been reported: carcinoma of the ovary, breast, stomach, lung, esophagus, colon, rectum, and kidney; sarcoma of bone; Hodgkin's disease, and multiple myeloma. Improvement in the clinical manifestations of dermatomyositis following radical or suppressive therapy of the tumor is of great practical significance. The initial impression gained from reading the literature is that a consistent improvement in symptoms of dermatomyositis is to be expected if suppression or cure of the malignancy is accomplished. Upon more extensive perusal of the literature, this view is not substantiated.

Systemic Lupus Erythematosus

I have left until the last a discussion of systemic lupus erythematosus. This malady is by all odds the most frequently encountered of the less common connective tissue disorders. Also, there is a greater probability of rheumatoid arthritis or acute rheumatic fever being confused with systemic lupus, particularly before the appearance of nonarticular symptoms of dissemination. In fact, a diagnosis either of rheumatoid arthritis or of acute rheumatic fever based upon satisfactory clinical evidence has been assumed in a significant percentage of patients who have died subsequently of disseminated lupus. Lupus has been misdiagnosed as one of a number of other diseases also. Included in this list are epilepsy; tuberculosis; acute glomerulonephritis; selected blood dyscrasias, particularly hemolytic anemia and thrombocytopenic purpura, and subacute bacterial endocarditis.

The increased incidence of systemic lupus, decade by decade, almost year by year, is an interesting matter for speculation. Whatever may be the etiology and pathogenesis of the incidence, surely it is on the increase, as demonstrated by the experience of Dubois,[8] who observed a fourfold increase over a period of three years.

Because lupus simulates rheumatoid arthritis or acute rheumatic fever so frequently in the earlier stages, I am of the opinion that it is desirable to inspect the peripheral blood for the presence of the L. E.-cell phenomenon in every patient suspected of suffering from either of these maladies. Admittedly this places a heavy load upon the hematology laboratory and tends to discredit the clinical acumen of the physician. Furthermore, it tends to overemphasize the phenomenon. I believe, however, that I will be vindicated eventually in advocating a search for L. E. cells routinely in every case of rheumatoid arthritis or acute rheumatic fever, preferably as early as possible in the course of the disease and at least once a year thereafter in active rheumatoid arthritis or more often should any variations from the anticipated normal course be observed. There are few physicians who would deny the desirability of a search for L. E. cells in a patient who presents atypical features of either of these maladies or whose clinical course is regressive in spite of good supportive treatment.

The probability of systemic lupus developing subsequently in patients with chronic discoid lupus is an important clinical item. The localized benign skin lesions of discoid lupus may be present in some patients for one or more decades before dissemination is recognized and clinical manifestations of systemic lupus develop. The dermatologists are more apt to see this phenomenon than we are, and in one series the incidence has been observed to be as high as 25%. In our experience a past history of discoid lupus is most unusual.

The cause of lupus has defied understanding, a characteristic of each of the connective tissue disorders. There is meager presumptive evidence in support of hypersensitivity. The definitive conclusions in favor of this explanation have not been established. There are three suggested items. A majority of patients with lupus are supersensitive to sun or to artificial ultraviolet rays. A severe reaction may follow a relatively short period of exposure, and ominous symptoms appear rapidly. Nor does a patient with lupus appear to develop tolerance to ultraviolet light in any stage of the disease. Some patients find that a few minutes of exposure to the sun may be devastating. A second item in the hypersensitive category is the appearance of a lupus-like clinical syndrome following ingestion of hydralazine, a widely used hypotensive drug. In a limited percentage of patients who have received this preparation the appearance of a lupus-like process was sufficiently disturbing as to raise the question as to the development of the classical entity. Fortunately, withdrawal of the drug results in subsidence of symptoms. A long follow-up, however, will be necessary before the danger is passed of the lupus-like entity

reappearing, and one is on safe ground in assuming that the disturbance was a temporary and reversible phenomenon. The third item refers to the appearance of the L. E. cell in the blood after a severe penicillin reaction and the disappearance after subsidence of other evidence of hypersensitivity.

There are yet two additional features that may be mentioned in this discussion of hypersensitivity, although not deserving of equal weight with the three just noted. The striking increase in incidence of systemic lupus during the past decade has followed the introduction and widespread use of antibiotics and other chemotherapeutic agents in the practice of medicine. It is purely speculative to draw any cause-and-effect conclusions. The coincidence, however, cannot be dismissed lightly. Also an anticomplementary serologic test for syphilis is a relatively common phenomenon in patients with lupus. This serologic finding is not to be confused with the biologic false-positive test that may appear in this malady.

The clinical characteristics are extremely varied. The classical picture of joint distress, unexplained malaise, fever, pallor, weight loss, and a butterfly rash on the face is not always observed. Usually the diagnosis is more difficult. The insidious development of symptoms which persist for weeks or months without offering more helpful clues is disturbing. The variegated picture presented early in the course of the disease has been discussed by Haserick and identified as the "L. E. diathesis."[9] This includes hypersensitivity to infections and drugs, photosensitivity, frequent episodes of pneumonia, emotional imbalance, and idiopathic epilepsy. Other features are visual disturbances, pleurisy, precordial pain, gastrointestinal symptoms, and complaints referrable to the genitourinary tract or the central nervous system. In the older literature effusion into the pleural cavity, abdominal cavity, and joint spaces was noted. These massive exudative phenomena are not seen as frequently now.

Several laboratory features, some specific and others nonspecific, are helpful in confirmation of the diagnosis. A hemolytic type of anemia, a positive Coombs' test, and an increase in the sedimentation rate have been observed. A leukopenia usually is present as well as a decrease in the number of circulating platelets. The serum globulin may be increased and the flocculation tests for liver function positive. The subject of false-positive serologic tests for syphilis has been a vital new aspect that has been injected into this problem in recent years.[10,11] The incidence of false-positive tests may be as high as 25%. If a positive serologic test is suspected of being biologically false, a treponemal immobilization test with a negative result confirms a false-positive presumption. It is important to appreciate that a number of patients with a chronic biologic false-positive serologic reaction have been shown to develop systemic lupus at a later date. In some patients several years may elapse between the detection of the false-positive test and the appearance of systemic symptoms. This observation has prompted Harvey and associates to presume that the natural history of lupus may be considerably longer, by years, than it was formerly thought to be.[12]

The most significant of the several procedures is the L. E.-cell phenomenon. In 1948, Hargraves and associates discovered this cell in the bone marrow of patients suffering from lupus.[13] At the present time a search of the peripheral blood usually reveals from the cells the clue that the patient is suffering from this malady.[14] The L. E. cell usually is a mature neutrophil comprising a reddish-purple staining inclusion body. This inclusion body consists of break-down products of nucleic acid derived from nuclear substances that formerly were integrates of neutrophils or lymphocytes in the blood. A second characteristic phenomenon found in the same preparation as the L. E. cell is the L. E. rosette. The rosettes are the conglomerates of normal-appearing white blood cells which surround

a reddish-purple-staining mass. Demonstration of the L. E. cell and the L. E. rosette is probably as specific a test as is available for the laboratory confirmation of clinical diagnosis. Most important in the detection of the L. E. cell is the experience of the microscopist. The incidence of positive results as reported in the literature varies from less than 50% to virtually 100%. The greater the number of times a test is applied in each suspected patient the higher the percentage of positive findings. Furthermore, a repeatedly negative L. E. search does not exclude the diagnosis, but most patients with well-developed lupus or those with an incomplete clinical picture and who subsequently show unmistakable clinical evidence of the malady exhibit this telltale finding upon careful examination.

It is pertinent to note that only a decade ago pathologists were skeptical of the specificity of the pathological lesions in systemic lupus. At the present time I believe that most pathologists agree that the clinical diagnosis may be confirmed microscopically from several or all of the specific structural alterations. Proliferation of the endothelial cells of the glomerular capillaries and hyaline thickening of the basement membranes creates the appearance of a "wire-loop" lesion.[2] Initially the material for demonstration of the "wire-loop" lesions was obtained postmortem. It is possible now to obtain valuable information from kidney slices extracted by trochar biopsy from patients suspected of suffering from lupus.[15] This may be an important diagnostic tool, particularly because of the relatively high incidence of kidney lesions in patients suffering from the systemic malady. Although changes similar to the wire-loop lesion may be observed in other types of kidney diseases, they are of sufficient specificity to be highly significant when the clinical signs point the way. Other morphologic findings at postmortem examination include periarterial fibrosis of the central arteries of the spleen, a nonbacterial endocarditis, hematoxylin-staining bodies in the heart, necrosis of lymph nodes, and interstitial changes in the parenchyma of the lungs.

There is no cure for this dread disease which seems to afflict persons of all ages. General measures as well as quasispecific agents have proven to be of great help, and we are always hopeful of current investigations if we are able to keep symptoms under control. Even though specific treatment is not now available, I believe that life has been prolonged and distressing symptoms kept under partial control by contemporary measures.[16] Nutrition may be maintained through the appetite-stimulating action of adrenal steroids. Physical rest during the acute phase of the disease is obligatory. The indiscriminate use of drugs should be avoided. Heart failure may be treated with a low-salt intake and suitable cardiac preparations. Unfortunately the low-salt diet is not particularly palatable, and one must weigh advantages versus disadvantages in this recommendation. Mild or severe infections should be sought out carefully and repeatedly and if found should be treated with appropriate antibiotics. Probably sulfonamides should be used only if other antibiotics are thought to be unsuitable as a result of sensitivity tests. The use of penicillin has been under some suspicion because of the incidence of hypersensitivity following its use as well as the appearance of the L. E. cell after penicillin administration. It has been noted by some observers that antibiotics are ineffective unless adrenal hormones are administered simultaneously. Particular attention should be paid to the avoidance of exposure to the sun or artificial ultraviolet radiation.

I believe that the administration of corticotropin (ACTH) or one of the adrenal steroids offers the most promising temporary help that we have at the present time. The mechanism of the therapeutic value has not been defined. Presumably the action is related to suppression of harmful enzymatic processes in affected cells rather than a result of the reversal of the basic dysfunction. It is the practice in our clinic to start

with fairly large doses of corticotropin initially and continue for a minimum of two or three weeks. A change to oral cortisone usually follows. Prednisone appears to be as effective as was hydrocortisone or cortisone, without as high an incidence of undesirable side-actions. Whether or not the latest available cortisone, triamcinolone (9-α-fluoro-16-α-hydroxyl-δ-*l*-hydrocortisone diacetate), will prove to be superior to prednisone, remains to be determined. We have had limited experience with this drug only in recent months and have observed no overwhelming advantages. The dose of adrenal steroids should be limited by the amount necessary to control symptoms or, failing this, up to the point of tolerance as determined by the development of Cushingoid features. Supplementary potassium, exchange resins, and oral or mercurial diuretics are helpful in maintaining water and salt equilibrium if there is a tendency to retention of these normal-occurring components.

Most of the patients seen in our clinic are maintained with steroids so long as symptoms are present. An attempt is made to control symptoms rather than to correct a laboratory abnormality. A majority of patients will experience an improvement in well-being, an increase in appetite, a gain in weight in addition to fluid retention, suppression of fever, and a more optimistic outlook. The usual contraindications to long-term steroid therapy in full pharmacologic doses should be heeded. L. E. cells sometimes are diminished during the remission; sometimes they disappear. Their disappearance does not mean that a cure has been achieved.

In addition to steroids, the antimalarials have gained considerable in favor during the past year. The clinical trial with antimalarials was based upon the beneficial affect of this group of drugs in patients with chronic discoid lupus. The mode of action may be related to reduction in light sensitivity of the skin. The antimalarials have been used singly or in combination with adrenal steroids. With a relatively low incidence of side-reactions, it is believed that these agents provide one more therapeutic approach to the management of this malady.

Conclusion

I shall conclude by cautioning you to suspect one of the less common connective tissue disorders, particularly systemic lupus erythematosus, in a patient with atypical features of acute rheumatic fever or rheumatoid arthritis or with persistent low-grade symptoms that do not respond to current therapeutic agents. The incidence of systemic lupus is increasing at an alarming rate and also, to a smaller extent, are the other less common connective tissue disorders, without a full understanding of the reason for these increases. They may be related to the tremendous expansion in number and use in clinical medicine or organic preparations, particularly the antibiotics. The recognition of these maladies is more exact now because of the discovery of the L. E. cell and the significance of skin and muscle biopsy. Treatment leaves much to be desired, however, and current investigations must be concerned with more effective means of therapy as well as a better understanding of the underlying pathogenic processes.

The University of Buffalo School of Medicine, Department of Medicine, 100 High St. (3).

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Use of Radioisotopes in the Diagnosis of Anemia

PHILIP C. JOHNSON, M.D.; ROBERT M. BIRD, M.D., and WILLIAM L. HUGHES, M.D., Oklahoma City

In the study of hematological disorders there has been great enthusiasm for the use of radioactive isotopes as investigative tools, but their application to clinical diagnosis has not been so readily accepted. At present the general concensus is that vitamin B_{12} labeled with cobalt 60, erythrocytes labeled with chromium 51, and iron salts labeled with iron 59 should supply information of importance in the clinical classification of anemias. It seems timely, therefore, to inquire whether these isotopic techniques supply information which is either unique, more accurate, or more readily measured than are conventional diagnostic procedures. To this end the experience in this laboratory with these radioactive compounds is presented. The evidence would suggest the following conclusions: 1. The measurement of the intestinal absorption of cobalt 60 vitamin B_{12} supplies information regarding the lack of gastric intrinsic factor in pernicious anemia which is not readily obtained by other means. 2. The rate of disappearance of radioactivity from the circulating blood following the injection of homologous erythrocytes labeled with chromium 51 supplies information of clinical value in approximately half of the patients in whom the possibility of a hemolytic anemia exists. 3. Studies in this laboratory employing iron 59 for clinical testing by measuring plasma-iron disappearance rates, erythrocyte-iron reappearance times, and intestinal absorption of iron have failed to supply data which cannot be obtained more readily by nonisotopic techniques.

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Present address of Dr. Hughes: University of Virginia Hospitals, Charlottesville, Va.

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Radioisotope Service and Department of Medicine, Veterans' Administration Hospital and University of Oklahoma School of Medicine and Hospitals.

Methods

Cobalt 60 Vitamin B_{12} Absorption Test.—An estimate of the intestinal absorption of vitamin B_{12} was obtained as follows. The vitiamin was given orally in a dose of either 0.2γ or 1.2γ. Each dose was labeled with 0.2μc of cobalt 60. Carmine red was ingested one day after the vitamin. Stools were pooled for counting until the dye appeared in the feces. The radioactivity excreted was measured and expressed as a percentage of the oral dose.[1] To insure blood levels of vitamin B_{12} greater than the binding capacity of serum, 1000γ of the stable vitamin were injected intramuscularly at the time of the oral feeding. Urines were pooled for 24 hours after ingestion and counted.[2] The radioactivity in the liver area was measured using a 4×3 in. (7.6×10.2 cm.) plastic scintillation crystal. Counting over the liver area was done on the fifth, sixth, and seventh days after ingestion. The daily counts were corrected for patient background[3] and averaged. All results were expressed as a per cent of the ingested radioactivity and do not represent absolute quantities.

Chromium 51 Labeling of Erythrocytes as a Measure of Hemolysis.—An estimate of red cell survival in the circulation was obtained by labeling erythrocytes with chromium 51 and transfusing them into the donor. The labeling technique has been reported previously by us.[4] One day and again eight days after the labeled cells had been transfused blood was drawn. The radioactivity per cubic centimeter of packed red cells in each sample was measured. The results were expressed as the per cent of radioactivity remaining on the eighth day. This method of expression correctly reflects the data obtained and avoids the use of the term "half-life," which reflects neither the half-life of erythrocytes nor the half decay time of chromium 51.

Results

Cobalt 60 Vitamin B_{12} Absorption Test.

Twenty-two patients having no evidence of hematological or neurological disease

TABLE 1.—*Normal Values in Cobalt 60 Vitamin B_{12} Absorption Test*

	Ingested Dose Recovered, %	
	Mean ± S. E.	Range (Mean ± 2 S. D.)
1.2 γ vitamin B_{12} containing 0.2μc Co^{60} (9 subjects)		
Stool	51±5.8	17–85
Urine	16±1.8	5.5–27
Liver	2.3±0.2	1.1–3.5
0.2 γ vitamin B_{12} containing 0.2μc Co^{60} (13 subjects)		
Stool	19±1.9	5.1–33
Urine	15±1.2	5.8–24
Liver	4.9±0.5	1.4–8.4

served as control subjects for the vitamin B_{12} absorption test. Nine of these patients received 1.2γ of vitamin B_{12} orally, and 13 received 0.2γ. The results of these tests are presented in Table 1. The means and standard errors of the means are tabulated in the first column so that the data may be subjected to statistical analysis. With the larger dose of vitamin B_{12} the per cent of radioactivity recovered in the stool is greater, a mean of 51% as compared with 19%. The per cent of radioactivity recovered from urine is not influenced by the oral dose of the vitamin. However, scintillation counting over the liver area shows a mean of 2.3% with the larger dose and 4.9% with the smaller. This difference in the liver values is significant statistically at the 0.001 level. It confirms Glass's work,[5] which showed that the percentage absorption of vitamin B_{12} is inversely proportional to the ingested dose. Therefore, we selected the 0.2γ dose of vitamin B_{12} (0.2μc cobalt 60) for routine diagnostic use. In the second column of Table 1 are presented a range of values which can be used in clinical testing. This range is obtained by using the mean plus or minus two standard deviations from the mean. Such a range is presented because it should include 95% of the test population and is considered as our normal range.

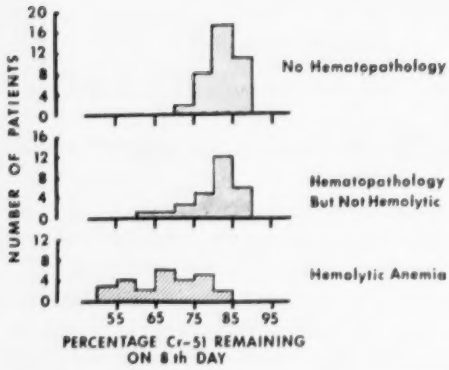
Six patients with pernicious anemia were similarly tested. The diagnosis was established without knowledge of the absorption data. The results are presented in Table 2 and are compared with our normal values. Only the range is given, since the mean is of no real value in clinical testing. The per cent of radioactivity recovered from the stools of patients with pernicious anemia is significantly greater than in normals. This would be expected, since the disease is manifested by a block in the intestinal absorption of vitamin B_{12}. Renal filtration and liver uptake of cobalt 60 vitamin B_{12} are significantly reduced in patients with pernicious anemia. Attention is called to the values obtained by scintillation counting over the liver area. The normal range for clinical testing is 1.4% to 8.4%, whereas in pernicious anemia it is 0.0% to 1.0%.

Chromium 51 Labeling of Erythrocytes as a Measure of Hemolysis.—The red cells from 38 patients without anemia or other evidences of a hematological disorder were labeled with chromium 51, and the per cent of radioactivity remaining on the eighth day was measured. The results in this group are presented as the upper section of the Figure. An additional 28 patients had disease of the hematopoietic system but showed none of the standard evidences of hemolysis. Their erythrocytes were labeled, and the per cent of radioactivity is shown in the middle section of the Figure. In the bottom section of this Figure are presented the results obtained in 26 patients who had obvious hemolysis. In these patients the increased hemolysis was due either to a congenital

TABLE 2.—*Co^{60} Vitamin B_{12} Absorption Test**

	Range of Ingested Dose Recovered (Mean ± 2 S. D.), %	
	Normals	Pernicious Anemia
Stool	5.1–33	45–100
Urine	5.8–24	0.2–6.8
Liver	1.4–8.4	0–1.0

* 0.2 γ vitamin B_{12} containing 0.2μc Co^{60} (see text).



defect of the red cells or to an acquired hemolytic process. The classification of the patients as grouped in the Figure was formulated on the basis of detailed hematological studies and without regard for the chromium 51 data. The normal group had a mean value of 83% of the initial radioactivity remaining on the eighth day. The middle group having disease of the hematopoietic system had a mean of 81% of radioactivity remaining. As would be expected, these two groups do not differ statistically (P greater than 0.1). The mean of the hemolytic group is 67%. This is different from each of the other means in a statistically significant fashion (P less than 0.001). The Figure illustrates the wide range of values obtained in these clinical groups, the spread being greatest in the two groups having hematological disease. Because of this wide distribution of values, there is presented in Table 3 a range of values which can be used in clinical testing. This range is obtained by using the mean plus or minus two standard deviations from the mean. It should be noted that 50% of the values in the hemolytic group fall within range of normal.

TABLE 3.—*Cr^{51}-Labeled Erythrocytes as a Measure of Hemolysis*

	Radioactivity Remaining, %	
	Mean ± S. E.	Range (Mean ± 2 S. D.)
Hematopathology, no hemolysis	81 ± 1.2	93–68
Hemolysis	67 ± 2.3	91–44

Comment

Our values for fecal and urinary radioactivity following oral feeding of labeled vitamin B_{12} generally agree with those in the literature.[1,6-8] Miller[9] reports much higher values for urinary excretion in normal subjects. Glass has written extensively[5] on scintillation counting over the liver as a measure of vitamin B_{12} absorption. For liver counting he employs a crystal 1 in. (2.5 cm.) in diameter, in contrast to the 4 in. (10.2 cm.) crystal used by us. Our values are eight times greater than those of Glass.[3,10] The 4 in. scintillation crystal undoubtedly accounts for this difference. We consider that our method of counting is technically simple and more nearly reflects the absolute quantity of radioactivity in the liver area. Liver counting eliminates the need for accurate collection of excreta. Therefore, for routine diagnostic use scintillation counting over the liver area is the most practical way to measure intestinal absorption of cobalt 60 vitamin B_{12}.

Two cautions in the interpretation of liver counting should be mentioned. In the first place, previous use of other radioactive compounds may cause high patient background which obscures the low counting rates characteristic of the vitamin B_{12} absorption test. This is particularly true in the patient who has previously received colloidal thorium dioxide (Thorotrast). Secondly, conditions other than pernicious anemia may also be associated with faulty absorption of vitamin B_{12} from the intestinal tract. These include the sprue syndrome, anatomical defects of the bowel, severe infections, and myxedema. Sprue and related disorders can usually be differentiated from pernicious anemia, since the simultaneous feeding of gastric intrinsic factor does not increase the absorption. The majority of patients with pernicious anemia can be diagnosed without recourse to isotopic techniques. There are three clinical situations, however, where this test is necessary for accurate diagnosis. The first is the patient with evidence of posterior

and lateral spinal cord dysfunction and without anemia. The second is the patient giving a history of pernicious anemia but in whom treatment has made the morphological diagnosis impossible. The third is in pernicious anemia of children, where gastric acid is a common finding. In the first two conditions withholding vitamin B_{12} therapy while awaiting a hematological relapse may result in permanent neurological damage. It is in these three clinical situations that the absorption test supplies unique information. It is unique because it will demonstrate the characteristic absorption defect of pernicious anemia. This defect is the result of a deficiency of gastric intrinsic factor and is not influenced by the administration of hematinics. If the test gives borderline values, repeating the test with the simultaneous feeding of whole gastric juice or commercial intrinsic factor will bring the test results into the normal range only in pernicious anemia. It would seem that the cobalt 60 vitamin B_{12} absorption test is a worthwhile addition to the laboratory methods now available for the diagnosis of pernicious anemia.

There are two quite separate problems which should be discussed before one attempts to evaluate the chromium 51 labeling of erythrocytes as a measure of hemolysis. The first concerns making the distinction between early senescence and random destruction of red cells. The second concerns the variability in the rate of hemolysis in a hemolytic anemia.[11] Under physiological conditions the red cell count reflects a balance between erythropoiesis and red cell death. The rate of red cell destruction may be increased in a random fashion without regard to age or by early senescence. Random destruction characterizes the symptomatic hemolytic anemias, while early senescence is usually present in conditions associated with a refractory anemia. In most instances the differentiation of anemia resulting from these separate mechanisms is not difficult and does not require isotopic techniques. When suboptimal rates of erythropoiesis complicate the clinical picture, standard laboratory procedures frequently fail to clarify the mechanisms. Here the chromium labeling technique will give useful information in approximately one-half of the cases.

The natural history of symptomatic hemolytic anemia is frequently characterized by marked variations in the rates of red cell destruction. Should the chromium test be performed at a time when the hemolytic process is relatively quiescent, values within the normal range are to be expected. We feel that this in part accounts for the wide spread of values encountered in our hemolytic group and suggest that retesting during a period of progressive anemia may clarify many borderline results.

Thus chromium labeling of erythrocytes is a relatively simple laboratory procedure; it is technically easier to perform than the Ashby technique,[12] and if used selectively it will give information of clinical importance in the identification of the hemolytic state. The occurrence of indecisive results does not invalidate the test but merely emphasizes the importance of interpreting any laboratory result in the light of the total clinical picture.

Summary

The clinical experience of one laboratory using two radioisotopes, i. e., cobalt 60 vitamin B_{12} and chromium 51-labeled erythrocytes has been reviewed.

The intestinal absorption of cobalt 60 vitamin B_{12} can be measured by determining the percentage of radioactivity excreted in the stool and urine or by the percentage of radioactivity present in the liver area. Each technique permits the identification of intrinsic-factor deficiency. In clinical studies, however, the vagaries of stool and urine collection are such as to make the scintillation count of the liver more practical. This technique has a high degree of accuracy in differentiating pernicious anemia from other anemias and is not influenced by previous vitamin B_{12} therapy.

Homologous erythrocytes can be labeled with radioactive chromium 51 and reinjected. Measurement of the per cent of radioactivity remaining on the eighth day gives information of clinical use in the diagnosis of the hemolytic state.

The University of Oklahoma School of Medicine, 800 N. E. 13th St. (4).

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Nitrofurantoin in Chronic Urinary Tract Infection

ERNEST JAWETZ, M.D., Ph.D.; JAMES HOPPER Jr., M.D., and DONALD R. SMITH, M.D., San Francisco

Nitrofurantoin (Furadantin) has recently become established as a useful drug in urinary tract infections. After oral administration it is excreted in the urine in sufficiently high concentrations to give strong antibacterial effects against many microorganisms which are commonly encountered in urinary tract infections. In spite of the demonstration of nitrofurantoin in the blood by chemical methods,[1] no significant antibacterial action in blood has been detected.[2] The lack of antimicrobial effect in the blood of persons receiving nitrofurantoin combined with the marked antimicrobial action in their urine defines this drug as a urinary antiseptic, i. e., a substance likely to suppress bacteria in urine but not in tissue. Many studies have dealt with the usefulness of nitrofurantoin in acute and uncomplicated infections of the urinary tract.[2-5] Daily doses of from 400 to 800 mg. continued for 3 to 12 days frequently result in the relief of symptoms and the suppression of bacteriuria and pyuria. While relapses occur with varying frequency, the great tendency toward healing of acute uncomplicated urinary tract infections makes results of nitrofurantoin treatment probably as satisfactory as those with any other antimicrobial agent.

In chronic urinary tract infection the picture is entirely different. The tendency to spontaneous complete healing is small, and the rate of relapse (and reinfection) after any type of drug therapy is very high. While many antimicrobial agents may temporarily suppress bacteriuria and symptoms, ultimate elimination of bacteria occurs in only about 10% of cases.[6] This holds true even when strongly bactericidal agents are given for prolonged periods of treatment.[7] More favorable reports are based probably on inadequate follow-up of patients.

Thus the physician treating a patient with established chronic urinary tract infection faces a grave problem of management. After repeated urological investigations, attempted correction of anatomical or functional disorders, and exhaustive attempts to eradicate the infection with antimicrobial drugs, he is often forced to admit defeat. He cannot cure the patient but can only try to maintain renal function and control symptoms referable to the urinary tract as well as possible. In the past sulfonamides have been used frequently and quite successfully to this end. Their prolonged administration probably is preferable to that of antibiotics. In view of the satisfactory short-term use of nitrofurantoin as a urinary antiseptic it was desirable to evaluate the potentialities of that drug in chronic urinary tract infection. The present paper attempts to answer, in part, the following questions:

(*a*) How effectively can nitrofurantoin suppress bacteriuria and lower urinary tract symptoms when administered in full doses for two weeks to cases of chronic urinary tract infection, and what proportion of patients will relapse?

(*b*) After initial suppression of bacteriuria, what will be the effect of continued administration of "maintenance doses" of nitrofurantoin (100-200 mg. per day for 2 to 12 months) on such patients? Can efficient suppression of bacteria in the urine—without

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From the Departments of Microbiology, Medicine, and Surgery (Urology), University of California School of Medicine. Professor of Microbiology, Lecturer in Medicine and Pediatrics (Dr. Jawetz); Associate Professor of Medicine (Dr. Hopper), and Clinical Professor of Urology (Dr. Smith).

antimicrobial action in tissue—lead to eradication of chronic infection in the kidney, or will withdrawal of the suppressive drug be followed by relapse?

(*c*) In patients with renal insufficiency associated with chronic infection, can prolonged suppression of bacteriuria preserve, or improve, renal function?

Materials and Methods *

Patients.—Thirty-two outpatients participated in the study. Each had chronic infection in the urinary tract established by past history and repeated bacteriological examination of the urine. Efforts were made to find an anatomical basis for the chronic infection through complete urological study, including intravenous and retrograde pyelograms. The renal function was estimated by determination of the nonprotein nitrogen or creatinine concentrations in the blood and endogenous creatinine clearance tests. After a patient had been selected for study an additional quantitative urine culture was secured at the start of treatment. The patient was given a fixed amount of nitrofurantoin and was questioned at each return visit about taking the prescribed amount of drug and about experiencing any side-reactions. Estimation of nitrofurantoin levels in the urine served as a check on drug intake. At each return visit urine specimens were secured for culture, and after appropriate clinical examination the patient was issued additional amounts of drug.

Drug Treatment.—Nitrofurantoin was used in the form of 50 or 100 mg. scored tablets or as oral suspension containing 25 mg. per teaspoonful.† For adults the initial dose was 400 to 600 mg. daily for one to two weeks, usually followd by a maintenance dose of 100 to 200 mg. daily for weeks or months. In children the daily dose ranged from 100 to 400 mg. No other antimicrobial agents were administered concurrently.

Laboratory Studies.—At each visit midstream urine specimens were collected aseptically for bacteriological examination and assay of nitrofurantoin concentration. From the first 20 patients blood serum was also secured.

Quantitative bacteriological cultures were immediately performed on all urine specimens as described elsewhere.[5] Serum and urine samples were stored at —20 C until nitrofurantoin assay could be performed. Bacteria isolated from the urine were tested for nitrofurantoin sensitivity as follows. Suitable amounts of nitrofurantoin 0.6% in polyethylene glycol 300 were added to proteose peptone No. 3 in broth (Difco) to give final concentrations of 30γ, 120γ, and 300γ per milliliter.[6] An equivalent amount of plain polyethylene glycol 300 in broth served as control. All broth tubes were inoculated with approximately 10^5 bacteria from a 24-hour broth culture and incubated for 24 hours. Tubes remaining clear after incubation were considered to contain an inhibitory concentration of nitrofurantoin. Subculture of such clear tubes usually yielded no growth, indicating that the inhibitory drug concentration was also bactericidal.

For assay of nitrofurantoin levels serial dilutions of urine were prepared in broth inoculated with a strain of Escherichia coli inhibited by 0.3γ per milliliter of nitrofurantoin. In control tubes the test organism was inoculated into known serial dilutions of nitrofurantoin in broth. Duplicate determinations agreed to within one or two twofold dilutions. We attempted to find antimicrobial activity in the serum of persons receiving nitrofurantoin. In the first 20 serum specimens obtained at the time of high urine levels of nitrofurantoin no inhibition of the nitrofurantoin-sensitive bacteria was found.[2] This determination was therefore abandoned.

Studies were undertaken in vitro to determine whether addition of nitrofurantoin increased the antimicrobial action of antibiotics. The techniques were the same as employed in many earlier studies

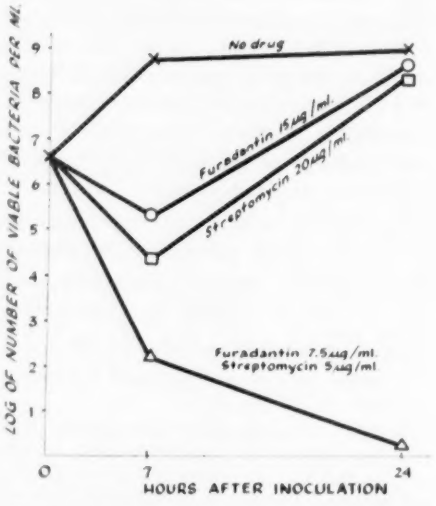

Fig. 1.—An instance of synergistic antimicrobial action between nitrofurantoin (Furadantin) and streptomycin acting on a strain of E. coli (Strain B. H.) in vitro.

* The following physicians participated in the care of these patients: Dr. B. Hymel, Dr. P. Lahr, and Dr. R. Oppenheimer.

† Supplied by Dr. George S. Rogers, Eaton Laboratories, Norwich, N. Y., who also provided the laboratory testing solutions.

TABLE 1.—*Patients with Chronic Urinary Tract Infection Who Received Nitrofurantoin for Fourteen to Nineteen Days*

Case	Infection Known, Yr.	Pretreatment			Nitrofurantoin Treatment			Urine Culture, Bact./Ml.	Post-Treatment Follow-Up		
					Dose		Urine Level				
		Urine Culture, Bacteria	No./Ml.	Nitrofurantoin Inhibition, γ/Ml.	Days	Mg./Day	γ/Ml.		Time Elapsed	Urine Culture Bacteria	No./Ml.
1	1	E. coli	10^8	300	15	500	60–120	0	3 mo.	Negative	
2	?	E. coli	10^8	30	14	600	60	0	2 mo.	Negative	
3	?	E. coli	10^7	15	14	300	15	0	1 mo.	E. coli	10^8
4	10	E. coli	10^8	30	14	600	240	0	2 wk.	E. coli.	10^8
5	?	Coliform	10^8	30	15	600	75	0	2 wk.	Coliform	10^8
6 (9 Yr.)	4	E. coli	10^7	30	14	100	240	0	1 mo.	E. coli	10^8
7	1	E. coli hemol.	10^7	300	14	400	15	0	2 wk.	E. coli hemol.	10^8
8	1	Aerobacter	10^7	?	15	400	?	0	1 mo.	Negative	
9	3	E. coli	10^8	120	14	600	120	10^4	2 wk.	E. coli	10^7
10	?	E. coli	10^8	30	19	400	?	0	5 mo.	Negative	
11	10	Coliform	10^8	30	14	400	20	0	2 wk.	Coliform	10^7
12	3	Aerobacter	10^8	300	18	400	60	10^7	2 wk.	Aerobacter	10^7
13	1	Pseudomonas	10^7	300	19	600	120	10^7	1 wk.	Pseudomonas	10^7

from this laboratory dealing with combined antibiotic action.[10,11] The results indicated that nitrofurantoin, if inhibitory at all, usually was strongly bactericidal and that consequently positive summation of drug action was difficult to demonstrate. One of the few instances in which apparent synergistic action occurred between streptomycin and nitrofurantoin is illustrated in Figure 1. This type of effect was observed so rarely that it could be discounted for practical purposes in selecting drugs for prolonged therapy.

Follow-Up Study.—Nitrofurantoin administration was discontinued after periods varying from a few days (if the patient did not tolerate the drug) to 17 months. After cessation of therapy the patient was reevaluated from the standpoint of general health and well-being, renal function, and bacteriological findings in the urine over a period of 2 to 20 weeks without drugs.

Results

Thirty-two patients participated in the present study. Six of them developed side-effects from nitrofurantoin in the first two to five days of treatment. These included repeated nausea and vomiting, epigastric burning or pain, and, in two patients, maculopapular pruritic skin rashes. The side-effects were sufficiently severe so that the drug was discontinued and these six patients dropped from the series. The remaining 26 patients are grouped according to the length of nitrofurantoin treatment.

A. Thirteen patients with subacute or chronic urinary tract infection received nitrofurantoin from 14 to 19 days, as summarized in Table 1. The daily dose in the 12 adults ranged from 300 to 600 mg.; in a 9-year-old girl it was 100 mg. All had infections due to Gram-negative bacilli, 12 of which were inhibited in vitro by 15γ to 300γ of nitrofurantoin per milliliter. The levels of drug in the urine fluctuated widely (from less than 15γ to more than 240γ per milliliter) and were not regularly related to the oral intake of the drug. While the patient was taking nitrofurantoin the urine culture was repeatedly negative in 10 and positive in only 3 persons, whose organisms were inhibited by 120, 300, and more than 300γ per milliliter, respectively. However, urine cultures became positive again soon after discontinuing the drug in six patients and remained bacteria-free for one to three months in only four persons. In every case the bacteria grown from the urine after treatment resembled the type recovered from that patient initially. Thus only 4 "cures" were observed in 13 patients treated with average doses of nitrofurantoin for 14 to 19 days.

B. Five patients received nitrofurantoin for five to nine weeks in total doses of 7.8 to 14.8 gm. Three persons had had well-established urinary tract infection for more than two years, but in the remaining two the duration was not well defined. Repeated urine cultures failed to reveal bacteria during treatment in four patients and for three to four months after discontinuing the drug in two patients. In one there was no complete suppression of the bacteria during therapy, and in two others the follow-up period of less than one month is not adequate to draw any conclusions.

C. Eight patients underwent prolonged nitrofurantoin treatment and are of the greatest interest (Table 2). All had long-established urinary tract infection previously treated by a variety of antimicrobial agents. Total amounts of 20.0 to 83.0 gm. of nitrofurantoin were taken over periods of 4 to 17 months. These patients tolerated the drug quite well. Repeated laboratory examinations of the blood did not reveal toxic drug effects.[12] The urine culture became negative during the initial nitrofurantoin treatment at full dosage (400 to 600 mg. per day) and remained negative during maintenance therapy (100 to 200 mg. per day) in all but one patient, who developed a superinfection with Proteus mirabilis (Case 21). After the drug had been discontinued one patient (Case 18) maintained a negative urine culture during the two months of her follow-up. Another patient remained negative for one week (Case 17); then nitrofurantoin was reinstituted because of his marginal renal function and great likelihood of reinfection. The other five patients yielded positive urine cultures in from four to eight weeks after

TABLE 2.—*Patients with Chronic Urinary Tract Infection Who Received Nitrofurantoin for Four to Seventeen Months*

Case	Infection Known, Yr.	Pretreatment Urine Culture, Bacteria	Nitrofurantoin Treatment					Post-Treatment Follow-Up		
			No./Ml.	Mo.	Total Dose, Gm.	Initial Dose, Mg./Day	Maintenance Dose, Mg./Day	Urine Culture, Bact./Ml.	Time Elapsed	Urine Culture Bacteria	No./Ml.
14	10	Coliform	10^6	13	78.2	200	200	0	1 mo.	Coliform	10^7
15	3	E. coli	10^6	4	31.2	400	200	0	1 mo.	E. coli	10^7
16	3	E. coli hemol.	10^6	5½	20.0	400	200	0	6 wk.	E. coli hemol.	10^7
17	1	Enterococci and Pseudomonas		12	48.1	150	150	0	1 wk.	Negative	
18	10	E. coli	10^6	4½	20.2	600	100	0	2 mo.	Negative	
19	3	Staph.	10^6	11	33.5	200	100	0	2 mo.	E. coli	10^7
20	23	Enterococci	10^5	14½	49.2	600	100	0	2 mo.	Enterococci	10^5
21	2	Coliform	10^6	17	83.0	200	100–400	0 then Proteus	2 wk.	Proteus	10^5

discontinuing nitrofurantoin maintenance doses. In four of these five cases the organism recovered after treatment (enterococcus, hemolytic E. coli, nonhemolytic coliform bacteria) appeared to be the same as that cultured prior to therapy. This would suggest the persistence of infection in tissue and shedding of bacteria after the antibacterial activity of nitrofurantoin had disappeared from the urine.

The eight patients in this group all suffered from symptoms of either lower or upper urinary tract infection or both when started on treatment. All were completely relieved of symptoms during the period of nitrofurantoin administration, except the girl (Fig. 2) who became superinfected in the course of drug treatment. That patient's course is given below in some detail (Case 21).

Three patients in this group were in marked renal failure. They suffered from "complicated" urinary tract infection: chronic pyelonephritis with staghorn calculi, polycystic kidney, or congenital deformity of renal pelvis with obstruction. It is of interest that in these patients renal function (as measured by creatinine clearance and nitrogen retention) was maintained well and perhaps even improved slightly during nitrofurantoin administration. This is illustrated by Case 17, given in detail below.

Report of Cases

CASE 21.—A 9-year-old girl had first exhibited symptoms suggestive of urinary tract infection two years previously, when she had developed frequency, enuresis, and burning on urination. Repeated courses of antimicrobial therapy gave only temporary improvement. During the administration of sulfonamides or tetracycline her symptoms disappeared, only to recur within one or two weeks after the drugs had been discontinued.

Physical examination was entirely within normal limits. Laboratory examination showed a hemoglobin of 11.8 gm. per 100 ml., a white blood cell count of 9300, and a normal differential count. Her renal function appeared adequate with the excretion of phenolsulfonphthalein of 45% in 45 minutes, and a blood nonprotein nitrogen of 30 mg. per 100 ml.

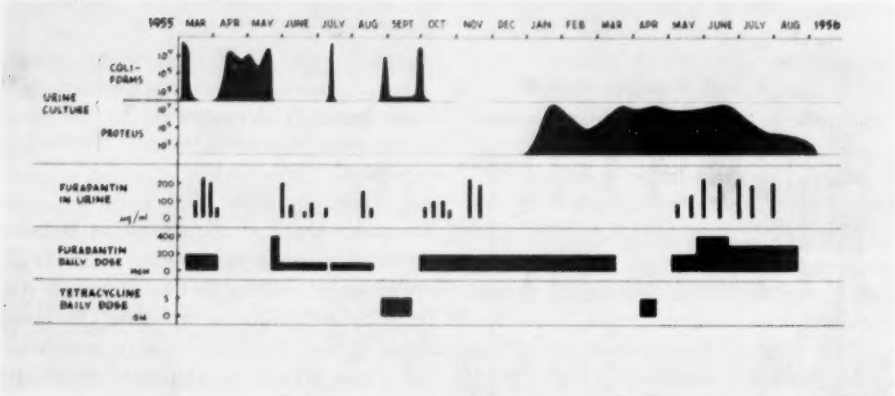

Fig. 2.—The course of Case 21, a 9-year-old girl with chronic urinary tract infection and possible bladder-neck obstruction.

Urological study revealed evidence of chronic cystitis on cystoscopy but no evidence of obstruction anywhere in the urinary tract. Excretory pyelograms indicated a bifid renal pelvis on the left but normal outlines of calyces. No residual bladder urine was found after voiding. Repeated cultures of the urine yielded E. coli in excess of 100,000,000 per milliliter of urine. The organism was completely inhibited by 15γ per milliliter of nitrofurantoin.

The patient received an initial course of nitrofurantoin of 200 mg. daily for 19 days. During this treatment urine cultures remained negative, but bacteriuria reappeared promptly when the drug was stopped. The subsequent treatment and course of the patient are depicted in Figure 2. Repeated courses of nitrofurantoin in daily doses from 100 to 400 mg. for varying periods of time were administered between March, 1955, and August, 1956. The patient ingested a total of 83.0 gm. of nitrofurantoin during this period and showed no ill effects from the drug in repeated laboratory examinations of blood and liver-function tests. However, superinfection of the urinary tract with Proteus mirabilis occurred in January, 1956, and this remained unaffected by subsequent treatment with tetracycline and nitrofurantoin.

Reinvestigation of the urinary tract in March, 1956, again showed chronic cystitis, but cystometrograms now also indicated some abnormality in bladder emptying and a residual urine of 40 ml. The kidney function continued to be excellent. Bacteriological cultures from the right kidney urine were sterile; urine from the left kidney contained P. mirabilis, 1000 colonies per milliliter, and the same organism was present in large numbers in the bladder urine. Because of probable bladder neck or urethral obstruction, urethral dilations were begun, and gradually the Proteus infection diminished. Urological consultants recommended a plastic operation on the bladder neck in an attempt to remedy functional bladder-neck obstruction, which favored continued infection.

Comment.—This case illustrates how nitrofurantoin may be used for protracted periods for the suppression of infection in the urinary tract, even in the presence of probable obstruction. It likewise illustrates that the nitrofurantoin effect is that of a urinary antiseptic, suppressing bacteria only within the urinary passages, not in tissue. Furthermore, it is an example of the type of superinfection commonly encountered in the course of prolonged antimicrobial therapy. It must be emphasized that nitrofurantoin employed in such a situation is in no way curative, yet it may be a useful drug because it may provide prolonged relief from symptoms and permit better selection of the proper time for surgical or manipulative procedures.

Case 17.—A 43-year-old male clerk entered the hospital because of abdominal and back pain and urinary symptoms for several months. Fourteen years earlier hypertension had been discovered which has persisted to date. One year ago polycystic kidneys were diagnosed, and urethral catheterization was followed by chill, fever, frequency, urgency and burning on urination, and severe back pain. Intermittent administration of various antimicrobial agents resulted in remission of these symptoms for short periods only. Recently there also developed nausea, anorexia, and recurrent episodes of high fever.

TABLE 3.—*Measurements of Renal Function in Case 17*

Date	Serum Creatinine, Mg./100 Ml.	Creatinine Clearance, Ml./Min.	Urine Cultures and Bacteria
Dec. 20, 1955	9.6	6.3	10*
Jan. 3, 1956	8.4	5.7	0
Feb. 25, 1956	6.6	15	0
May 7, 1956	6.0	27	0*
July 31, 1956	6.0	27	0*
Oct. 15, 1956	6.4	20	0*
Jan. 2, 1957	5.6	20	0*

* Culture obtained after omitting nitrofurantoin dose for 5 to 8 days.

On admission the temperature was 39.5 C (103.1 F); the blood pressure, 160/90, and the respiratory rate, 32. There was bilateral flank tenderness. Laboratory examination revealed a hemoglobin of 8.7 gm. per 100 ml. and a white blood cell count of 18,000, with 75% polymorphonuclear leukocytes. The urine had a specific gravity of 1.004 and contained 4+ protein, many white cells, some red cells, and casts. A urine culture indicated many enterococci and Pseudomonas. The blood nonprotein nitrogen was 98 mg. per 100 ml.; the serum creatinine, 9.6 mg. per 100 ml., and the creatinine clearance, 6.3 ml. per minute (normal, 70 to 140 ml. per minute). Serum electrolytes were as follows: sodium, 133 mEq. per liter; chloride, 107 mEq. per liter, and carbon dioxide 11.2 mEq. per liter. The diagnosis was polycystic kidney, with hypertension, pyelonephritis, and renal insufficiency. Course: Treatment consisted initially of fluids and base-yielding electrolytes to correct acidosis, blood transfusion, reserpine, oral sulfonamides (6 gm. daily), then chloramphenicol (2 gm. daily), and polymyxin B intravenously (150 mg. daily for 10 days). The patient's uremia decreased, and the urinary tract infection appeared to be suppressed. Because of the minimal renal function and the great risk of persisting or recurring infection, he was given 100 to 150 mg. of nitrofurantoin daily for the next year. All subsequent cultures of the urine were negative. Measurements of renal function during this period indicated maintenance of function or possibly slight improvement (Table 3).

During this period the patient was feeling quite well and pursuing a normal life.

Comment.—Active chronic infection contributes greatly to renal insufficiency in patients whose kidneys are damaged by other causes. Intensive antimicrobial therapy frequently suppresses the infection but rarely eradicates it. When cure is impossible, long-term suppression of the infection may improve the residual kidney function, prevent symptoms of uremia, and enable the patient to continue a near-normal existence. In this patient nitrofurantoin accomplished this aim well. During one year of suppressive treatment the renal function was relieved of the additional impediment of active infection and returned to its "true" level.

Comment

Treatment of chronic urinary tract infection with antimicrobial drugs results in eradication of the infection in only a small proportion of patients. In all other such patients bacteria are found again in the urine some time after a given course of antimicrobial therapy, provided follow-up is sufficiently long. When rechecked two or three months after antimicrobial therapy, at least three-fourths of all such patients are found to have bacteriuria again. However, after antimicrobial therapy the symptoms referable to the urinary tract may be suppressed much longer than the bacteriuria. The physician then must decide whether to continue treating an asymptomatic patient, knowing that such treatment will continue only to suppress bacteriuria without permanently eradicating the infection.

The present study indicated that nitrofurantoin is a drug which is useful in chronic as well as in acute infections of the urinary tract. It is apparently not present in the blood in an active form and thus acts only as a urinary antiseptic. In contrast to some earlier studies,[3,4] most patients relapsed quite promptly after the drug was discontinued. However, during the period of drug administration symptoms were controlled as bacteriuria was suppressed. In addition certain patients with renal insufficiency derived measurable benefit from prolonged nitrofurantoin treatment; as infection was suppressed their renal function improved. This effect was sufficiently pronounced to be con-

sidered an important component of the management of uremia accompanying chronic pyelonephritis.

Study of the patients who took nitrofurantoin for long periods showed that chronic infection in the renal parenchyma persisted despite bactericidal concentrations of antimicrobial drugs in the urine, and after many months of suppression relapses promptly occurred when the drug was withdrawn. It was also of interest that in most instances the organisms recovered from the urine prior to nitrofurantoin treatment were so similar to be considered identical with those isolated after months of treatment.

These findings confirm the belief that a "urinary antiseptic," no matter how strongly antibacterial its action in the urine or how long it is taken, is not likely to eradicate the infection in the interstitial tissue of the kidney in chronic pyelonephritis. Unfortunately it is not known at present whether a bactericidal drug which produces high blood and tissue levels will be any more capable of achieving cure than a urinary antiseptic. However, in treating acute pyelonephritis systemically active bactericidal drugs are unquestionably better than urinary antiseptics.

The results of this study suggest that long-term administration of nitrofurantoin in chronic pyelonephritis may be advantageous, particularly in the presence of renal insufficiency. However, in the presence of probable, or demonstrated, obstruction in the urinary tract such long-term dosage seems rather futile. In such cases superinfection (as seen in Case 21) must be expected frequently, and the apparent success (i. e., suppression of symptoms) should not delude the physician into abandoning his repeated efforts to demonstrate and remedy functional or anatomical obstruction.

The number of patients in the present study was too small to permit an evaluation of the toxic hazards of such long-term nitrofurantoin administration. It is of interest that all patients who developed significant side-effects did so with doses of more than 200 mg. daily and experienced unpleasant symptoms within the first few days of nitrofurantoin treatment. One case of apparent hemolytic reaction tentatively attributed to the drug by others [12] likewise occurred early. Conversely, there were no complaints from any of the persons taking less than 200 mg. daily and none after the second week of treatment. Laboratory examinations likewise failed to reveal evidence of toxicity in the few persons who took from 20.0 to 83.0 gm. of the drug in 4 to 17 months. Thus the risks of such extended treatment do not appear great.

Summary

Nitrofurantoin was administered to patients suffering from chronic urinary tract infection either for short periods (14 to 19 days) or for 4 to 17 months. During nitrofurantoin treatment bacteria could not be cultured from the urine in most cases, but bacteriuria recurred soon after the drug was discontinued. The suppression of bacteriuria was associated with relief from symptoms, and, in some cases with severe renal insufficiency, it resulted in measurable improvement in renal function. Unpleasant side-effects developed in 6 of 32 patients during the first few days of nitrofurantoin administration. However, the ingestion of maintenance doses (100 to 200 mg. daily) for weeks and months was well tolerated by others. The protracted administration of nitrofurantoin to patients with ineradicable urinary tract infection, particularly chronic pyelonephritis without demonstrable obstruction, may usefully complement the medical management of this difficult problem.

University of California Medical Center, 3d & Parnassus (22).

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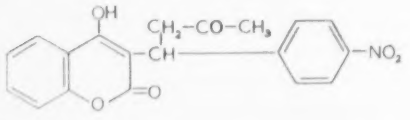
Clinical Experience with the Anticoagulant Acenocoumarin (Sintrom)

FRANCE ALEXANDER, M.D.; J. L. KOPPEL, Ph.D.; P. M. ARSCOTT, M.A., and JOHN H. OLWIN, M.D.,
Chicago

Thromboembolism and thromboembolic diseased states continue to be one of the major problems of clinical medicine. The potential hazards of thrombotic episodes and the frequent sequelae of chronic phlebitic processes render the effective use of anticoagulant drugs an increasingly important part of the clinician's therapeutic armamentarium. Such use is dependent upon the availability of anticoagulant drugs with clinically dependable pharmacological properties and on reliable assay procedures by which therapy with such drugs can be followed and controlled. A number of prothrombin depressants have been developed in the past 15 years, and of these, acenocoumarin (Sintrom) is one of the more recent ones. It is a nonhygroscopic light crystalline powder which is odorless and tasteless and is supplied for clinical use as 4 mg. scored tablets. It is stable under normal storage conditions and reacts as a weak acid. Chemically it is 3-(α-acetonyl-4-nitro-benzyl) 4-hydroxycoumarin.



Previous reports on acenocoumarin have described its lack of toxicity and its rapid action in depressing plasma prothrombin concentrations.[1-9] They also have stressed the relatively stable control levels resulting from its administration and the early disappearance of effects following its withdrawal. In addition, they have reported prompt and adequate reversal of its prothrombin depressant ability with different vitamin-K-active preparations.

The purpose of this paper is to report our clinical experience with 90 patients who were maintained with acenocoumarin therapy. Plasma prothrombin levels were followed with the one-stage and two-stage prothrombin assays in parallel. In a number of instances, additional prothrombin determinations were also carried out with the recently described TAMe (*p*-toluenesulfonyl-l-arginine methyl ester) assay.[10] The effects of the drug on plasma Ac globulin (Factor V), SPCA (Factor VII), and autoprothrombin II (Factor IX, PTC) were studied in a small group of patients.

Methods and Materials

Blood was collected by the two-syringe technique, nine parts being added immediately to one part of 3.2% sodium citrate. All prothrombin analyses were made within four hours of the collection of blood, whereas Ac globulin, Factor VII, and autoprothrombin II determinations were carried out on plasma samples which had been stored at —40 C for a period of up to two months. The results of the modified two-stage prothrombin assay of Ware and Seegers[11] were used to control the administration of acenocoumarin. The one-stage assay of Quick[12] was run in parallel, thromboplastin (Soluplastin*) being used in place of rabbit-brain extract. The TAMe assay for prothrombin was carried out according to the procedure of Glueck, Sherry and Troll.[10] Ac globulin was

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From the Department of Surgery, Presbyterian-St. Luke's Hospital. Affiliated with the University of Illinois College of Medicine.

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* Soluplastin was supplied by Schieffelin & Company, New York.

measured by the two-stage method of Ware and Seegers,[13] as modified by Olwin.[14] Factor VII was determined by the cothromboplastin assay of Mann[15] and the proconvertin procedure of Owren.[16] Autoprothrombin II (PTC) assays were carried out in the laboratory of Dr. Walter H. Seegers, Wayne State University College of Medicine, by the method of Johnson and Seegers,[17] and detailed results of this work are being reported in a separate paper.[18]

The patients were selected from the wards of the Cook County† and Presbyterian-St. Luke's hospitals and from the outpatient clinic of the latter. Among the 90 patients were a number from the fracture wards, without thromboembolic disease. Those with thromboembolism included patients with myocardial infarction, thrombophlebitis and phlebothrombosis, thrombophlebitis migrans, basilar and internal carotid artery thrombosis, and peripheral atherosclerosis obliterans. The patients' ages ranged from 19 to 66 years. Other patients in addition to the 90 were given acenocoumarin,‡ but since, for various reasons, they were not followed through the induction, maintenance, and recovery stages, they are not included in this report.

The drug was given first in small single doses, and the patients' prothrombin levels and general clinical conditions were observed for a period of days. The initial dosage was gradually increased until the routine of continuous daily doses was estabilshed. At the outset, all patients were hospitalized, but, as the study progressed, a number of them were treated on an outpatient basis, being recalled for prothrombin determinations at intervals of two days to two weeks. Once therapeutic levels were obtained (10% to 30% of normal), prothrombin levels were determined at intervals considered necessary in the individual case.

The periods of therapy ranged from 11 to 490 days, with a total of 4853 patient days. Nine of the patients are being maintained with therapy at the time of writing. Six patients received varying single doses of 12, 16, 20, 24, 28, and 32 mg., respectively, and were then followed through induction and complete recovery. The two patients who received 12 and 16 mg. doses, respectively, had histories of excessive alcohol intake, and the control prothrombin levels prior to initiation of therapy were below the normal range.

In order to study the ability of vitamin-K-active substances to reverse the effects of acenocoumarin, 15 patients were given various vitamin-K-active preparations as the drug was withdrawn, their prothrombin at the time being at control levels. A single 50 mg. dose of phytonadione (vitamin K_1 [Mephyton §]) was received orally by five different patients and intravenously by two others. For intravenous administration emulsions of the drug were prepared in 30 and 50 ml. of saline, respectively. One patient was given 75 mg. of vitamin K analogue ‖ intravenously, two patients received 72 mg. of menadione sodium bisulfite (Hykinone ¶) intravenously, and a fourth patient received 216 mg. of menadione sodium bisulfite by the same route. Both drugs were given in single doses in all cases. One patient received 50 mg. of vitamin K_1 orally, followed by five successive daily oral doses of 10 mg. Five other patients were given oral doses of 10 mg. of vitamin K_1 for eight sucessive days.

Effects of Varying Loading Doses of Acenocoumarin

Varying loading doses were administered daily to six patients until their plasma prothrombin levels were depressed to within the therapeutic bracket. One-stage and two-stage prothrombin determinations were carried out during the induction and recovery periods. The results obtained are summarized in the Table. The induction periods were found to be longer in the patients receiving initial doses of 12 and 16 mg., despite lower control prothrombin levels prior to the initiation of therapy. (These patients had histories of excessive alcohol intake.) Initial doses of 24, 28, and 32 mg. resulted in induction periods of identical duration. The 20 mg. initial dose, although resulting in the shortest induction time, of 36 hours, probably does not represent an optimal loading dose but rather an individual

Relationship Between Loading Dose and Observed Induction Time

Loading Dose, Mg.	Induction Time, Hr.	
	1-Stage	2-Stage
32	60	84
28	60	84
24	36	84
20	36	36
16	132	132
12	132	132

† Through the Department of Therapeutics, Hektoen Institute for Medical Research, of the Cook County Hospital.

‡ Supplied by Geigy Pharmaceuticals, Ardsley, N. Y.

§ Mephyton was supplied by Merck & Co., Inc.

‖ The Vitamin K analogue was supplied by The Upjohn Company.

¶ Hykinone was supplied by Abbott Laboratories.

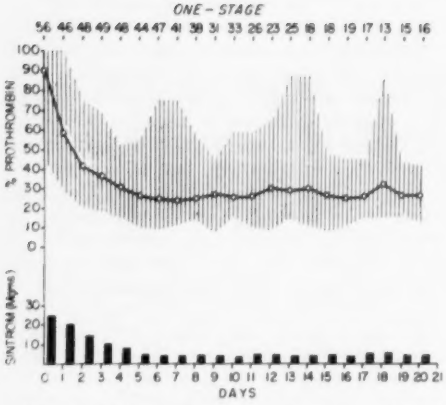

Fig. 1.—This graph represents a composite of the prothrombin levels observed during the induction and maintenance periods in 58 patients receiving acenocoumarin (Sintrom). The average levels and the extremes are shown for each day, as well as the corresponding average of acenocoumarin dosage. By both the one-stage (this graph) and the two-stage (Fig. 2) methods average control is obtained on the fifth day, though in some instances it is reached as early as 12 hours following the administration of the first dose of the drug. (The loading dose was usually given about 7 p. m. the day of the initial prothrombin reading and blood drawn about 7 a. m. the following morning.) Since prothrombin levels were not measured for all patients every day, the figures at the top of the graph represent the number of patients making up the composite for each day.

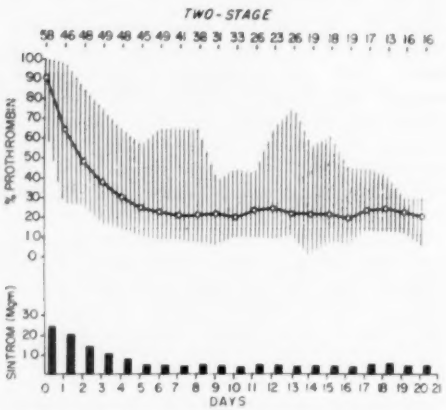

Fig. 2.—This graph represents a composite of the prothrombin levels observed during the induction and maintenance periods in 58 patients receiving acenocoumarin (Sintrom). The average levels and the extremes are shown for each day, as well as the corresponding average of acenocoumarin dosage. By both the one-stage (Fig. 1) and the two-stage (this graph) methods average control is obtained on the fifth day, though in some instances it is reached as early as 12 hours following the administration of the first dose of the drug. (The loading dose was usually given about 7 p. m. the day of the initial prothrombin reading and blood drawn about 7 a. m. the following morning.) Since prothrombin levels were not measured for all patients every day, the figures at the top of the graph represent the number of patients making up the composite for the day.

rapid response which occasionally occurs in therapy. Various other patients have received 32 mg. loading doses without any uniformly significant demonstrable decrease in the induction period.

Maintenance Therapy

The prothrombin levels of 58 patients were reduced to within the therapeutic bracket, maintained there for varying periods up to three weeks, and then allowed to return to normal. Figures 1 and 2 represent the induction and maintenance prothrombin levels as brought about by average doses of acenocoumarin. The average time required for achieving a therapeutic prothrombin level as determined by the one-stage was found to be between 84 and 108 hours, the most rapid induction time observed being 12 hours. Identical results were obtained with the two-stage method, although the drop during the first two days of therapy was less rapid than that measured by the one-stage assay. Common doses on the second, third, fourth, and fifth days during induction were 20, 14, 10, and 8 mg., respectively. Average daily maintenance dose of the drug was between 4 and 5 mg.

Recovery Period

The data plotted in Figures 3 and 4 represent the average prothrombin levels of 45 patients following withdrawal of the drug. Within 24 hours the average prothrombin level as determined by both one-stage and two-stage methods rose above the therapeutic range. There was a rapid rate of recovery during the first six days, with a more gradual return to normal from that point on. Pretherapy levels were attained within approximately 12 days. The rapid rise to levels above the therapeutic bracket constitutes both an advantage and a dis-

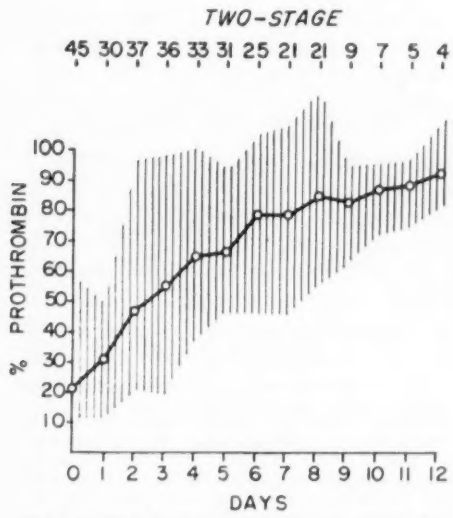

Fig. 3.—This graph represents the composite prothrombin levels obtained with the two-stage method as observed in varying numbers of patients following withdrawal of the drug. Again, the extremes for each day are plotted to indicate the spread obtained. As in Figures 1 and 2, the two-stage curve lags slightly behind the one-stage curve. Day zero on the graph actually represents 12 hours after discontinuation of the drug, Day one 36 hours after cessation of drug therapy, etc. By the sixth and seventh days the prothrombin values were up to 80% and then climbed more slowly to the precontrol values, reaching pretherapy levels by the 12th day.

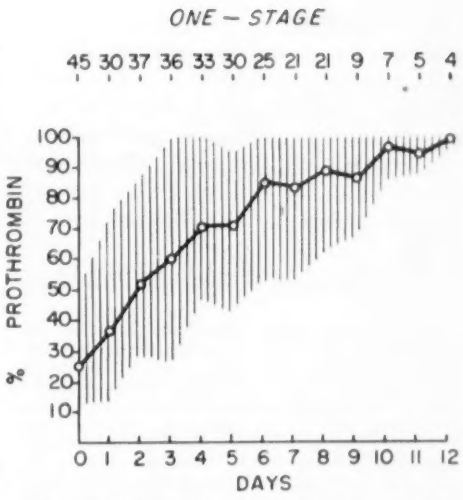

Fig. 4.—This graph represents the composite prothrombin levels obtained with the one-stage method as observed in varying numbers of patients following withdrawal of the drug. Again, the extremes for each day are plotted to indicate the spread obtained. As in Figures 1 and 2, the two-stage curve lags slightly behind the one-stage curve. Day zero on the graph actually represents 12 hours after discontinuation of the drug, Day one, 36 hours after cessation of drug therapy, etc. By the sixth and seventh days the prothrombin values were up to 80% and then climbed more slowly to the precontrol values, reaching pretherapy levels by the 12th day.

advantage in anticoagulant therapy. Thus, if a maintenance dose is omitted on any given day because of a low prothrombin level, the latter may have risen above the therapeutic bracket by the time the next sample is taken, 24 hours later. This occurred in a number of patients in this series (Fig. 5). The occurrence of uneven maintenance levels can be prevented by administering small doses of the drug (2 mg.) even when the prothrombin level is low, rather than by omitting the daily dose entirely. It was not found necessary in any instance to divide the daily dose of acenocoumarin. An obvious advantage of the rapid rise of prothrombin to levels above the therapeutic bracket is found in case of hemorrhage, unexpected trauma, or in the event that surgery becomes necessary during anticoagulant therapy.

Countereffects of Vitamin K

Figure 6 illustrates the changes in prothrombin levels found as a result of the administration of vitamin-K-active preparations. The time required for the prothrombin concentration to rise above the therapeutic range was about 20 to 24 hours by both assay methods. This was observed with all patients except one, who had received 216 mg. of menadione sodium bisulfite intravenously. Despite the higher dosage, it required 37 hours for his prothrombin to reach a level above 30% of normal. Prothrombin concentrations of 60% were reached most rapidly (52-56 hours) in patients receiving 50 mg. of phytonadione orally followed by five successive doses of 10 mg. each. One patient, who received 72 mg. of menadione sodium bisulfite intravenously, had the slowest rise to the 60% level, requiring 72 hours. Prothrombin levels

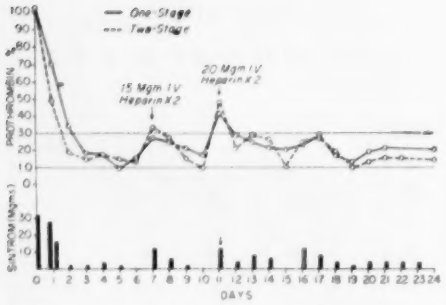

Fig. 5.—This graph depicts the induction and maintenance course of a patient given acenocoumarin (Sintrom) following a severe myocardial infarction. The solid line represents one-stage, the dotted line, two-stage prothrombin values. It can be readily seen that on two days when no acenocoumarin was given the values for prothrombin rose rapidly to above the therapeutic range by the following morning, necessitating heparin injections to insure adequate control. However, on the 19th day, with prothrombin values of 9%, (two-stage) and 13% (one-stage), 2 mg. of acenocoumarin was given, preventing such a sharp rise. This "escape" occurred in a number of patients on several occasions until we became familiar with the clinical effects of the drug. It is interesting that in this patient the prothrombin level by the two-stage assay dropped more rapidly than by the one-stage, and under varying doses of the drug fluctuations were wider. This emphasizes the variable responses of different patients to the same anticoagulant drug and the importance of careful individual control.

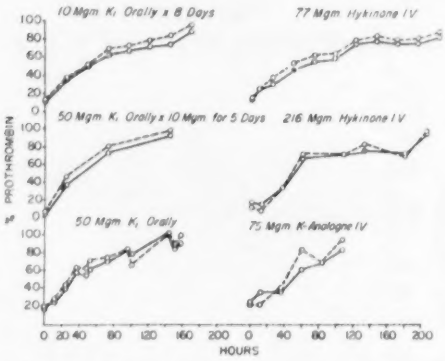
10 Mgm. K, Orally x 8 Days
77 Mgm. Hykinone I.V.
50 Mgm. K, Orally x 10 Mgm. for 5 Days
216 Mgm. Hykinone I.V.
50 Mgm. K, Orally
75 Mgm. K-Analogue I.V.
PROTHROMBIN %
HOURS

Fig. 6.—The above curves represent one-stage (dotted lines) and two-stage (solid lines) prothrombin levels of patients receiving various vitamin-K-active preparations. Day 0 represents the time of administration of the vitamin K preparation and also represents the point of 12 hours post discontinuance of the drug (the drug was discontinued the evening prior to administration of the vitamin K preparations). See text for discussion.

of 80% were attained most rapidly in patients receiving single 50 mg. doses of phytonadione orally or 50 mg. orally, initially followed by five daily successive oral doses of 10 mg. It required 120, 132, and 120 hours, respectively, to achieve levels above 80% in patients given, respectively, 72 mg. of menadione sodium bisulfite intravenously, 216 mg. intravenously, and eight daily successive oral doses of 10 mg. of phytonadione. The prothrombin elevation observed in patients receiving phytonadione intravenously was at a less rapid rate than in those patients who received the same preparation orally. This may have been due primarily to the fact that the nutritional state of the latter group of patients was somewhat below normal. In all cases studied the initial rate of recovery was rapid, with the final rise to normal levels being a more gradual one. The smoothest recovery was observed as a result of the daily oral administration of 10 mg. of phytonadione.

All vitamin-K-active substances tested were found effective in reversing the prothrombin-depressing effect of acenocoumarin. However, the properties and observed clinical effects of this drug make it unlikely that patients whose therapy is carefully controlled will require administration of vitamin-K-active substances to elevate their prothrombin levels. The prompt rise of plasma prothrombin following withdrawal of the drug should be adequate countermeasure in most instances.

Effects on Clotting Factors Other than Prothrombin

In eight patients the level of Factor VII decreased rapidly as a result of acenocoumarin administration. It closely followed the one-stage prothrombin values both during the induction period and following withdrawal of the drug.

In six patients the concentration of plasma Ac globulin was decreased as a result of acenocoumarin therapy, although not quite as rapidly as that of Factor VII. It usually reached levels between 5% and 25% of normal within four or five days following

initiation of therapy. After withdrawal of the drug, the level of Ac globulin returned to normal at approximately the same rate as the prothrombin as measured by the one-stage method.

In 14 patients in which autoprothrombin II (PTC, Christmas factor) was measured, this factor was found to decline at approximately the same time as prothrombin, although to a greater degree. Thus, when the latter was within the therapeutic bracket, the level of autoprothrombin II was usually near zero. Following withdrawal of the drug the level of autoprothrombin II remained depressed for 24 to 48 hours following initiation of prothrombin recovery.

Observations with TAMe Prothrombin Assay

The TAMe assay for prothrombin was carried out on 23 of the patients in the study. Nineteen of the twenty-three patients were followed from the beginning of induction to complete recovery, while spot checks were made on the remaining four. This series involved a total of 190 duplicate determinations which were carried out simultaneously with the two-stage and one-stage assays.

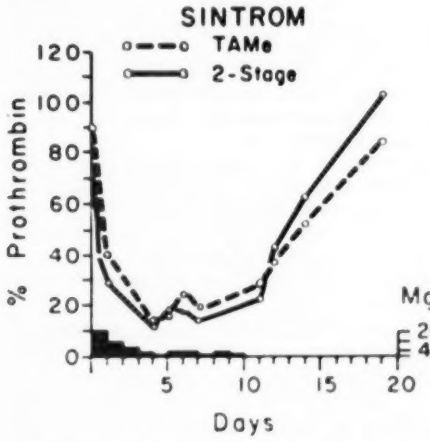

Fig. 7.—The data plotted in this graph represent TAMe and two-stage prothrombin values as observed in a patient given acenocoumarin (Sintrom) therapy. The results of the two methods parallel each other closely and are representative of the comparative values obtained in most of the patients on whom the TAMe assay was carried out.

Figure 7 represents the results of the TAMe and two-stage assays in a patient on short-term acenocoumarin therapy. With few exceptions all patients compared showed a similar close relationship of TAMe to two-stage results. From these data it is apparent that the TAMe assay is well suited for use in the control of acenocoumarin administration.

Therapeutic Effects

The therapeutic effects in patients receiving acenocoumarin for various thromboembolic conditions were similar to those achieved with other anticoagulant drugs. This is as would be expected, since the effects of acenocoumarin on various coagulation factors are similar to those of other drugs.

Toxicity and Complications

No side-effects or untoward reactions from acenocoumarin administration were observed. Liver function tests carried out on six patients following completion of drug therapy were normal. These tests included determinations of total protein, albumin-globulin ratio, sulfobromophthalein retention, icterus index, and prothrombin by both one-stage and two-stage assays. Bone marrow biopsies were done on nine patients following drug therapy from 2 to 12 months' duration. No depression of hematopoietic activity was observed. One patient developed gross hematuria seven weeks after initiation of therapy. His one-stage prothrombin at the time was 33%, and his two-stage prothrombin was 17%. He was at home when the bleeding developed and was given 50 mg. of phytonadione orally after a blood sample was taken. His bleeding stopped three days later, when his prothrombin had risen to 76%. Clinical findings supported a diagnosis of urethritis.

Summary

Acenocoumarin (Sintrom) was administered to 90 patients both with and without thromboembolic disease.

Acenocoumarin was found to be an effective and safe prothrombin depressant,

therapeutic levels of prothrombin being attained, on the average, within 5 days, with some individual induction periods being as short as 12 hours.

Following withdrawal of the drug, prothrombin rises in most instances to above 30% of normal within 36 hours. Eighty per cent prothrombin levels are attained in 6 to 7 days, and pretherapy levels, within 12 days.

The rate of recovery is hastened by the oral or intravenous administration of water-soluble or fat-soluble vitamin-K-active preparations.

In addition to its effect on prothrombin, acenocoumarin was observed to depress the levels of Factor VII, Ac globulin, and autoprothrombin II.

The TAMe (*p*-toluenesulfonyl-l-arginine methyl ester) assay for prothrombin was found to be well suited as a means for controlling administration of acenocoumarin.

Liver function tests and bone marrow biopsies gave no evidence of toxic effects. In the 90 patients studied bleeding was observed in only one instance. This was present as gross hematuria and occurred while the prothrombin was within the control bracket; it was attributed to a urethritis.

Presbyterian-St. Luke's Hospital, 1753 W. Congress St. (12) (Dr. Olwin).

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The Effects of Molar Sodium Lactate in Reversing the Cardiotoxic Effect of Hyperpotassemia

SAMUEL BELLET, M.D., and FRED WASSERMAN, M.D., Philadelphia

The subject of hyperpotassemia has assumed considerable importance in recent years. An excess of potassium produces profound disturbances in the organism in general and the heart in particular. The condition can be diagnosed relatively simply by clinical means, including the electrocardiogram, and may be confirmed by chemical determination. Hyperpotassemia kills primarily as a result of its cardiac effect, and this can, in most cases, be reversed by the various methods to be described below. Early recognition and prompt institution of proper therapy are of primary importance. The presence of hyperpotassemia may be said in many instances to constitute an acute cardiac emergency.

The causes of hyperpotassemia include those conditions which lead to an increase in the extracellular potassium which the patient is unable to handle, generally because of renal insufficiency. The increase in extracellular potassium may be the result of the following factors: (*a*) increased tissue destruction, anoxia, the crush syndrome, and intravascular hemolytic reactions; (*b*) acidosis, which results in a shift of potassium from the intracellular to the extracellular phase; (*c*) oliguria and anuria with inadequate excretion of potassium; and (*d*) dehydration and shock, which are often associated with the conditions mentioned above and result in concentration of the extracellular fluid, anoxia, and decreased renal function.

The electrocardiographic evidence of cardiac toxicity in hyperpotassemia is of extreme importance. Although the electrocardiogram may not parallel the serum level, it is in many ways of somewhat greater significance, since a specific increase in the serum level may lead to various degrees of cardiac toxicity. For example, a serum level of 7.0 mEq. per liter may result in Stage 2 intoxication in one patient, while in another the toxic effects may be more marked (Stage 3).[1] Tolerance depends on many factors, some of which have as yet not been determined. The electrocardiogram depicts the summation of those factors which affect the heart, which ultimately is the organ of paramount importance.[2] Death may occur at serum levels ranging from 8 to 12 mEq. per liter.

The object of this presentation is to report our experience in 11 cases of hyperpotassemia. In nine of these cases the evidence of cardiac toxicity was quite marked, and the electrocardiographic disturbance was of a type that suggested that cardiac arrest was threatened, if not actually imminent (Figs. 1A, 1B, 3, 5, and 6). In most of the patients reversal of the toxic cardiac effects was of considerable benefit; often, however, the underlying renal dam-

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Director, Division of Cardiology, Philadelphia General Hospital, and Director, Division of Cardiovascular Disease, Graduate Hospital of the University of Pennsylvania (Dr. Bellet); Fellow of the American Heart Association, Philadelphia General Hospital, and Instructor in Cardiology, University of Pennsylvania Graduate School of Medicine (Dr. Wasserman).

From the Division of Cardiology of the Philadelphia General Hospital and the Graduate Hospital and Robinette Foundation of the University of Pennsylvania. This work was aided by grants from the U. S. Public Health Service (Grant H 146C7) and the Foundation for Cardiovascular Research. The molar sodium lactate used in this study was furnished by Eli Lilly & Company, Indianapolis.

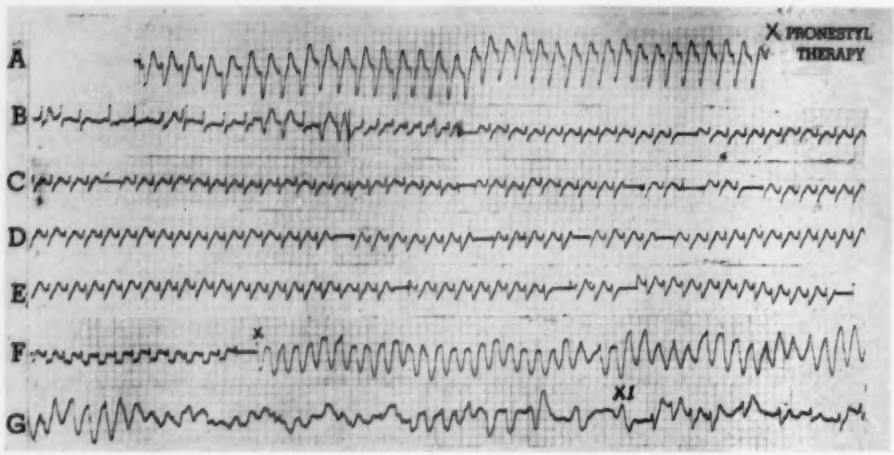
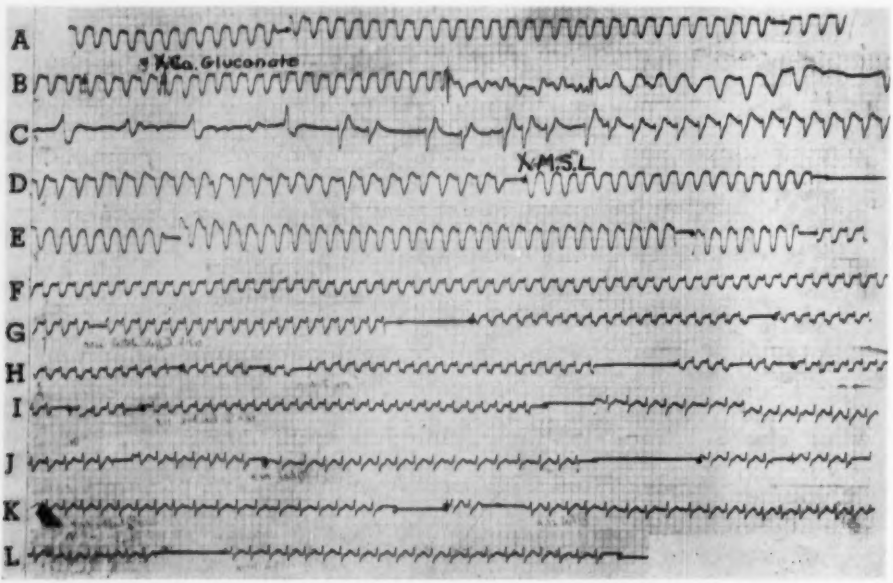


Fig. 1A (Case 1).—*A*, note paroxysmal tachycardia (ventricular?) with widened QRS before procainamide therapy. *B*, after procainamide therapy (375 mg. in 20 minutes intravenously) *B* to *E*, continuous strip after procainamide therapy. Note return to normal rhythm with narrower QRS width than in *A*. However, toward the end of *D* and *E* the QRS widened again. Note increased widening of QRS in *F*. The degree of aberration increased to *G*. The portion from *X* in Strip *F* to *XI* in strip *G* manifests ventricular flutter to ventricular fibrillation.

Fig. 1B.—Calcium gluconate given (20 cc. of a 10% solution) at *X*. *B*, note transient narrowing of QRS, which persisted for about 24 seconds, but marked aberration returned *D* to *F*. Molar sodium lactate was started at 4:03 p. m. at *D*. A total of 160 cc. of molar sodium lactate was administered in 30 minutes. Note gradual narrowing of QRS, with ST segment depression and return to a relatively normal configuration at end of *I*. Note normal width of QRS and normal T and *K* and *L*. This normal configuration continued and was maintained.



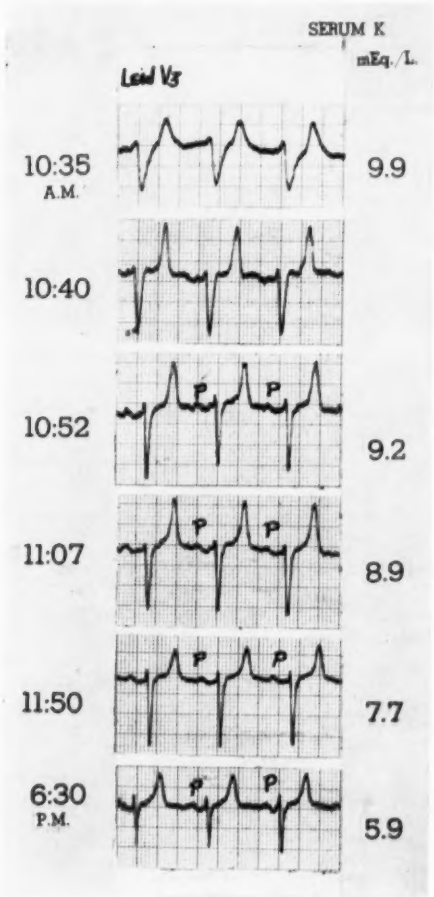


Fig. 2 (Case 2).—June 4, 1955. Tracing at 10:35 a. m. (serum K, 9.9 mEq. per liter, note widened KRS to 0.16 second and absence of P waves; 10:40 a. m. (after 150 cc. of M. S. L. given), note narrowing of QRS to 0.08 second, peaking of T waves and return of P waves; 10:52 a. m. (after 300 cc. of M. S. L. in 17 minutes), note still further narrowing of QRS with return of P waves; 11:07 a. m. (serum K, 8.9 mEq. per liter), note continued improvement; 11:50 a. m. (serum K, 7.7 mEq. per liter), note narrowing of QRS with P waves present; 6:30 p. m. (serum K, 5.9 mEq. per liter), note still further narrowing in QRS, with less peaking of T waves and shorter P-R interval.

age was of such severity that it was incompatible with life. Of the 11 patients to be reported, 5 patients died within 7 days of treatment with molar sodium lactate (M. S. L.), 4 additional patients died within 8 to 30 days following treatment, and 2 patients survived and were discharged from the hospital.

In order for treatment to be effective, particularly in the stage of advanced potassium poisoning, it is important to have a preparation which acts rapidly (in reducing the serum potassium concentration), is dependable, and is relatively nontoxic. In our experience, molar sodium lactate has proved to be the most satisfactory method of treating hyperkalemia exclusive of extracorporeal hemodialysis. The report of the 11 cases follows.

Report of Cases

Case 1.—A 51-year-old Negro woman was admitted to the Philadelphia General Hospital on Aug. 25, 1955, because of dyspnea, ankle edema, weight loss, weakness, and anorexia. There was a one-month history of frequent vomiting, occasionally of coffee-ground material. The diagnosis was hypertensive cardiovascular disease with uremia. She received treatment for the acidosis and azotemia from Aug. 26 to Sept. 16, and there was gradual clinical improvement, with a corresponding decrease in the blood urea nitrogen (BUN) from 180 mg. per 10 ml. on admission to 66 mg. per 100 ml. On Sept. 16 she complained of severe precordial pain, which was accompanied by a state of shock. The electrocardiogram taken at that time was suggestive of an acute anteroseptal myocardial infarction. Treatment consisted of anticoagulants and, because of slowly developing congestive heart failure, digitalis. Following the shock the BUN slowly rose, with a concomitant fall in the CO_2 combining power; the serum potassium gradually increased. On Oct. 16, 1955, following a convulsive seizure, the patient stopped breathing, and no heart sounds were audible. While artificial respiration was being given the patient was connected to the electrocardiogram, and ventricular tachycardia flutter was observed (Fig. 1A). No blood pressure reading was obtainable. In spite of intravenous procainamide (Pronestyl) (375 mg. in 20 minutes) and calcium gluconate (2 gm. of a 10% solution), no sustained improvement was noted. M. S. L. was then started at 4:03 p. m. A total of 160 cc. of M. S. L. was administered in 30 minutes. After the last 40 cc. of M. S. L. (given in seven minutes), the electrocardiogram showed a return to a normal rhythm; the blood pressure slowly rose to 170/85. The patient was then given 120 cc. of M. S. L. intravenously within the next 24 minutes, which apparently was sufficient to induce and maintain a relatively normal electrocardio-

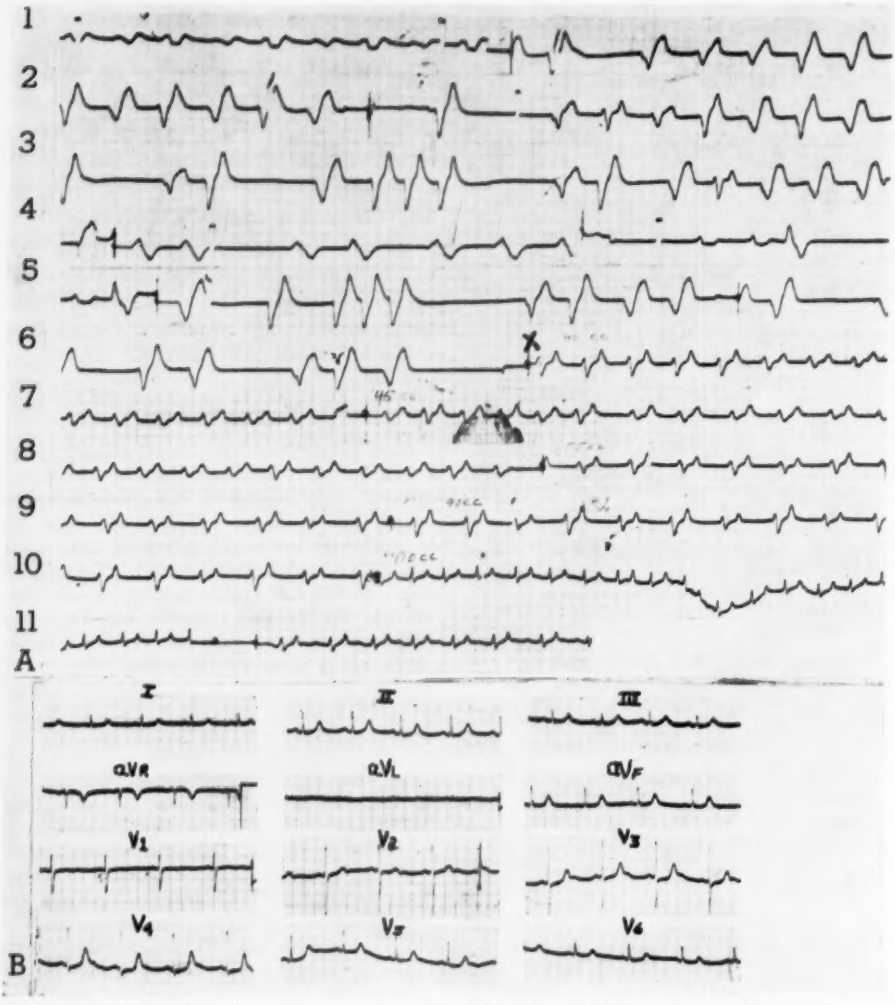


Fig. 3 (Case 3).—*A*, continuous tracing. Note the widened QRS complexes with irregular cycle length with absence of P waves. The complexes from 1 to 4 resemble those of the dying heart. Forty cubic centimeters of 2.5 M sodium lactate (100 mEq.) was administered slowly up to *X* in Strip *6*. Thereafter, 2.5 M sodium lactate was continued until a total of 110 cc. had been administered. Within 60 seconds the previously widened QRS complexes measuring 0.20 to 0.24 second were narrowed to 0.16 second, and within 20 minutes sinus rhythm was restored. Coincident with return of the electrocardiogram to a more normal configuration with normal conduction there was marked improvement in the patient clinically. Note the return of relatively normal electrocardiographic pattern at the end of Strip *10* and in Strip *11*. *B*, on the following day, note the relatively normal electrocardiogram, aside from slight peaking of the T waves.

graphic pattern. (Fig. 1B,*L*.) The blood pressure remained at a level between 150 to 170 mm. systolic and 70 to 85 mm. diastolic. No further episodes of ventricular tachycardia or flutter occurred. The patient, however, continued oliguric, and by Oct. 19 the BUN had increased to 180 mg. per 100 ml. and the serum potassium to 9.2 mEq. per liter. Subsequently the patient was treated with M. S. L., calcium gluconate, cation exchange resins, and daily hypertonic dextrose infusions. This program resulted in a gradual decrease in the serum potassium to 5.4 mEq. per liter on Oct. 21. The BUN, however, continued elevated (180 mg. per 100 ml.); the patient's

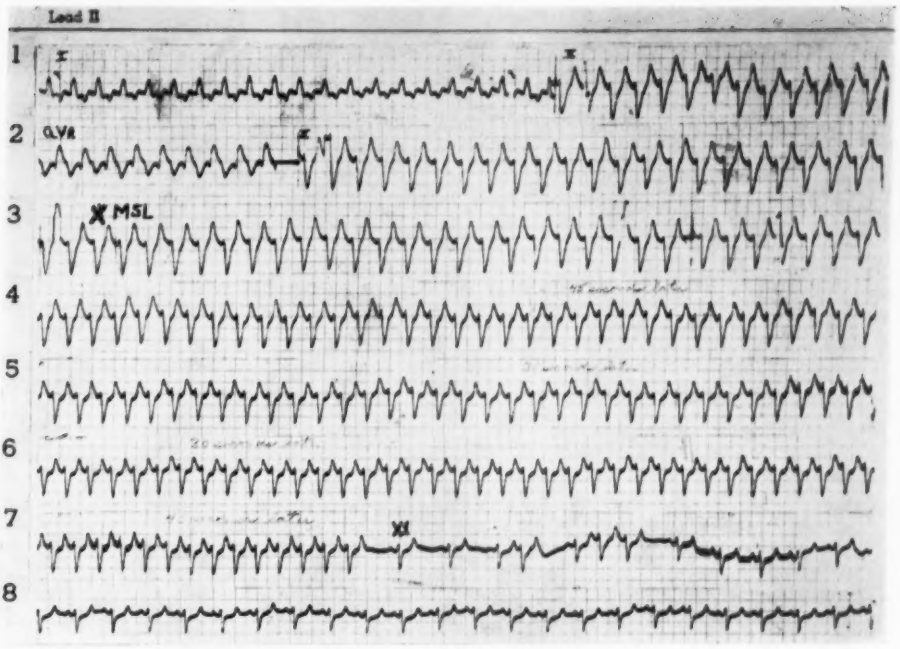


Fig. 4 (Case 6).—The serum potassium is 7.6 mEq. per liter. Strips *1* and *2* show short portions of Leads I, II, and aV_R. Toward the middle of Strip *2* the lead is changed again Lead II. Subsequently, Strips *2-8* are essentially a continuous record. In Strips *1* and *2* note the appearance of a tachycardia (supraventricular?) with a rate of 140 per minute. The QRS complexes are widened, measuring approximately 0.18 second. The T waves are tall, and no P waves are discernible (text). At *X* in Strip *3* forty cubic centimeters of 2.5 M sodium lactate is given intravenously as rapidly as possible (in 30 seconds). This is followed by progressive narrowing of the QRS complexes in Strips *4*, *5*, and *6*. At *XT* in Strip *7*, following a pause, sinus rhythm develops with a slower ventricular rate (80 per minute). In Strip *8* the sinus rhythm is established with a ventricular rate of approximately 96 per minute. The QRS complexes have narrowed to 0.08 second.

clinical state gradually deteriorated, and on Oct. 30, 1955, she died. Blood-chemistry findings and serum electrolyte levels are recorded in Table 1.

CASE 2.—A 63-year-old white male alcoholic was admitted to the Philadelphia General Hospital on June 2, 1955, with a history of recently drinking "Sterno," shaving lotion, cleaning fluid, and rubbing alcohol. For the past six weeks he had experienced repeated bouts of hematemesis and diarrhea, which was intermittently tarry.

Examination revealed a generalized tremor and marked generalized hyperesthesia; a few scattered rales were audible at both bases. There was no cardiomegaly, and no murmurs were heard; the blood pressure was 138/80. The patient's urinary output appeared adequate. In view of his relatively poor oral intake and evidence of dehydration, supplementary intravenous fluid which contained a total of 2.98 gm. of potassium chloride was given on the morning of June 3, 1955. On the afternoon of June 3, 1955, the electrocardiogram suggested potassium intoxication. At this time the serum potassium was 7.8 mEq. per liter; sodium, 130 mEq. per liter; CO_2 combining power, 15 mEq. per liter; blood sugar, 143 mg. per 100 ml., and BUN, 11 mg. per 100 ml.; urinalysis showed a trace of protein, 20-25 WBC per high-power field, and 3-5 coarsely granular casts.

On June 4, 1955, the patient appeared mentally obtunded, the blood pressure had dropped to 105/65, and his clinical state appeared very poor. The serum K had risen to 9.9 mEq. per liter at 10:35 a. m. (Fig. 2). The electrocardiogram was characteristic of the third stage of hyperkalemia. The QRS complexes were widened to 0.16 second, and no P waves were visible. Following administration of 300 cc. of M. S. L. in 17 minutes there was almost immediate clinical improvement accompanied by a return of the previously widened QRS complexes to normal (Fig. 2). During this time the serum potassium had decreased to 7.8 mEq. per liter at 11:30 a. m., and by 6:30 p. m., to 5.9 mEq. per liter.

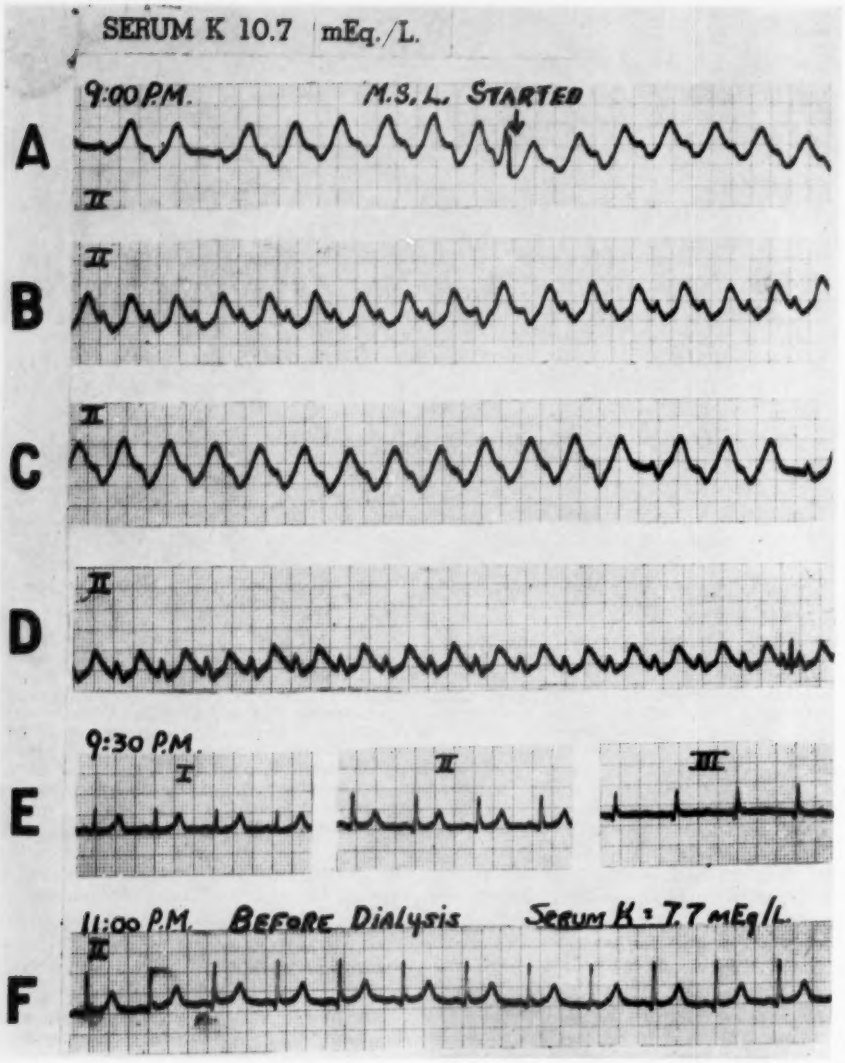


Fig. 5 (Case 7).—Strip *A* (Lead II), taken at 9:00 p. m., when the patient was in coma and circulatory collapse. Bizarre idioventricular beats resembling ventricular flutter are present. The serum potassium was 10.7 mEq. per liter. Molar sodium lactate was started slowly as indicated. Lead II (Strip *B*), taken at 9:10 p. m. after 60 mEq. of molar sodium lactate was given intravenously in 10 minutes. The rhythm still appears to be ventricular flutter but is somewhat less bizarre. Strip *C*, taken at 9:14 p. m. after 50 cc. of 50% dextrose with 80 units of regular insulin had been given intravenously at two minutes previously. No additional lactate was given. Note further deterioration of the complexes (Lead II), compared to Strip *B* above. Strip *D* (Lead II), taken at 9:25 p. m., five minutes after an additional 110 cc. of molar sodium lactate was given rapidly in two minutes. The QRS complexes have narrowed significantly; the ventricular rate is regular at 137 per minute. No P waves are discernible. Strip *E*, taken at 9:30 p. m., shows Leads I, II, and III. Sinus rhythm has been restored. The rate has slowed to 100 per minute. The QRS complexes have narrowed to approximately 0.06 sec. Strip *F* (Lead II), taken at 11:00 p. m., shows a relatively normal electrocardiogram. The Q-T interval (0.36 second) is slightly prolonged for the heart rate.

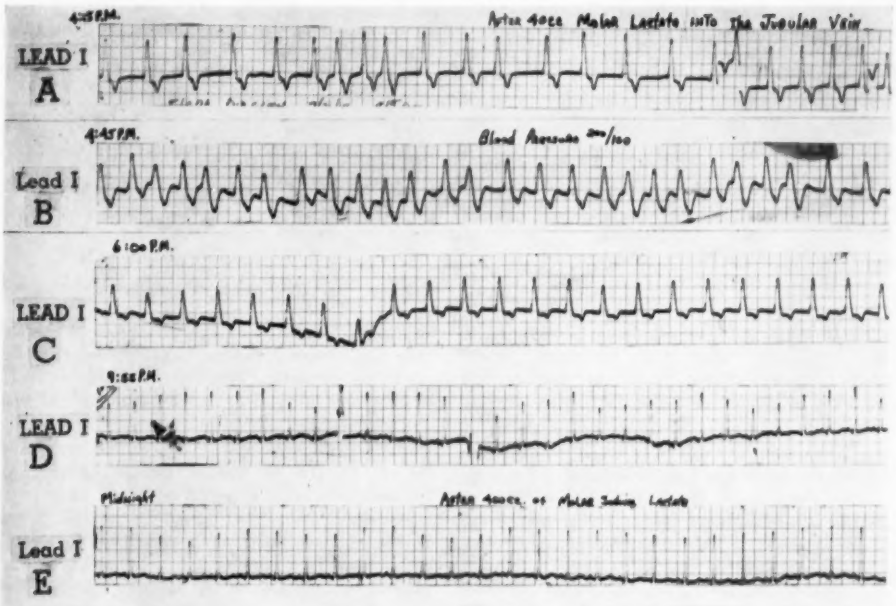


Fig. 6 (Case 8).—This 51-year-old hypertensive patient with uremia had suddenly developed circulatory collapse and become comatose approximately five minutes before Strip *A*. Strip *A*, the control cardiogram (Lead I), taken immediately after 40 cc. of M. S. L. had been given slowly into the jugular vein, shows an irregular idioventricular rhythm with widened QRS complexes measuring 0.12 second in width. There is marked RS-T segment depression, and the T waves are deeply inverted. Strip *B* (Lead I), taken at 4:45 p. m. The blood pressure has gradually increased to 200/100. No additional lactate has been given. Note the further QRS widening, which measures 0.16 second, and the more marked RS-T segment depression. The ventricular rate is irregular. A 425 cc. infusion of M. S. L. had been prepared and was started intravenously after this strip. Strip *C* (Lead I), taken at 6:00 p. m., after approximately 225 cc. of sodium lactate. The QRS complexes have narrowed to 0.12 second; there is less RS-T segment depression, and the T waves are less deeply inverted. The ventricular rate has become regular at 97/minutes Strip *D* (Lead I), taken at 9:55 p. m., after approximately 320 cc. of sodium lactate. Note the appearance of sinus tachycardia (rate, 125 per minute), marked narrowing of the previously widened QRS complexes, which now measure 0.06 second in width, and the low but upright T wave. The Q-T intervals is prolonged for the rate and suggests the presence of hypocalcemia. Strip *E* (Lead I), taken at midnight after 400 cc. of M. S. L. had been given. The blood pressure has maintained a relatively normal value since 4:45 p. m., and the patient has gradually become oriented. By 10:30 p. m. she was able to relate a detailed history.

At noon on June 5, 1955, the patient developed a transient atrial fibrillation with a ventricular rate of 100 per minute; on June 7, 1955, normal sinus rhythm returned spontaneously. Thereafter, the patient's electrolyte state tended to improve, and following a marked diuresis he developed hypokalemia which was treated with potassium. His condition gradually improved, and on July 11 he was discharged from the hospital in good condition. The administration of M. S. L. to this patient at a critical period was largely responsible for his ultimate recovery.

The final diagnosis was acute and chronic alcoholism with evidence of renal damage, liver damage, gastroenterocolitis, acidosis, azotemia, and hypocalcemia. The blood chemistry and serum electrolyte data are recorded in Table 2.

Case 3.—A 61-year-old white man was admitted to the Hospital of the University of Pennsylvania on Dec. 10, 1955, because of "bloody urine" of 18 hours' duration. The patient was first told he had "kidney stones" in 1932 but had refused more than symptomatic treatment. Except for recurrent attacks of renal colic, he had remained in apparently good health. In April, 1952, he was hospitalized for a herniorrhaphy and found to have chronic lymphatic leukemia. Treatment consisted of total body (spray) irradiation, multiple blood transfusions, cortisone, and x-ray therapy directed toward reducing a greatly enlarged spleen. In spite of this, his course was progressively downhill. The x-ray therapy to the spleen was completed on Dec. 9, 1955, the day preceding admission.

TABLE 1.—*Blood Chemistry and Serum Electrolyte Findings in Case 1*

Date	CO_2, mEq./L.	Cl, mEq./L.	Na, mEq./L.	K, mEq./L.	BUN, Mg./100 Ml.	Ca, Mg./100 Ml.
10/13	23.4	79.8	123	8.0	90	
10/16			125	9.6		
10/17	29.3	84.1	136	8.5	112	
10/19			130	9.2	180	
10/21			140	5.4		6.6
10/22	26.1	84.1	140	7.0	180	
10/24	9.0	82.0	130	5.4		

Some 18 hours prior to admission he experienced right renal colic followed by hematuria. A detailed systemic review failed to disclose any symptoms of congestive failure or angina pectoris.

Physical examination revealed a chronically ill man in no acute distress. The blood pressure was 110/70; the pulse was 100 per minute and regular. The chest was clear. The heart was normal in size, and no murmurs were heard. The tip of the spleen extended down to the umbilicus. There was no hepatomegaly. Marked costovertebral angle tenderness was noted on the right side.

Initial laboratory examination disclosed a hemoglobin of 9.6 gm. per 100 ml. The white blood cell count was 2000, with 40% neutrophils and 60% lymphocytes; the platelet count was 10,000 per cubic centimeter. The urine showed a dense flocculation of albumin, with many red and white blood cells. The blood urea nitrogen was 72 mg. per 100 ml. A chest x-ray showed only a kyphoscoliotic deformity of the thoracic spine; a flat plate of the abdomen showed three renal calculi on the right, an enlarged spleen, and some loss of stature on the 12th dorsal vertebra. The patient was treated symptomatically; the hematuria appeared to be spontaneously diminishing. His appetite was good, and his fluid intake and urinary output were adequate. On Dec. 14, 1955, patient developed sudden vascular collapse: he became pale and clammy, and no blood pressure reading could be obtained. The electrocardiogram taken at that time (Fig. 3*A*) showed markedly widened QRS complexes and an absence of P waves, suggesting hyperpotassemia. The patient was given 90 cc. of 2.5 M sodium lactate (225 mEq.) intravenously over a period of about 15 minutes, followed by 20 cc. (50 mEq.) in 10 min. Within several minutes there was a return of the electrocardiogram to a normal sinus rhythm and marked clinical improvement in the patient. His sensorium cleared, and he became alert and cooperative. The slow, irregular pulse speeded and became regular. Approximately two hours after instituting therapy the serum potassium was 7.1 mEq. per liter. Subsequently, he was treated with small amounts of M. S. L. daily, calcium, hypertonic dextrose, and insulin. Although clinical and electrocardiographic improvement (Fig. 3*B*) was dramatic, the patient required vasopressors to maintain his blood pressure. He continued critically ill and died on Dec. 18, 1955, in severe congestive failure. Serum electrolyte levels and blood chemistry findings are charted in Table 3.

CASE 4.—A 19-year-old Negro woman, was known to have had hypertension (blood pressure 180/120) since the age of 14, when she developed preeclampsia during her pregnancy. She was ad-

TABLE 2.—*Blood Chemistry and Serum Electrolyte Findings in Case 2 on June 3, 1955*

Time	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	BUN, Mg./100 Ml.	Ca, Mg./100 Ml
6/3/55	130	7.8				
6/4/55						
10:35 a.m. (before lactate)	153	9.9	88	15	11	7.4
10:52 a.m. (after 300 cc. of M.S.L. given)	156	9.2	85	17		7.2
11:07 a.m.	165	8.9	83	18		7.5
11:32 a.m.	157	8.8	83			7.3
11:50 a.m.	157	7.7	84	21		7.4
6:30 p.m.	156	5.9		26		

TABLE 3.—*Blood Chemistry and Serum Electrolyte Findings in Case 3*

Date	BUN, Mg./100 Ml.	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	Ca, Mg./100 Ml.	Uric Acid, Mg./100 Ml.
12/12	72					9.7	31.6
12/13		148	7.1	89	17.1	10.0	38.9
12/14		137	7.0	87	30.9	7.2	
12/15 (a.m.)		137	3.6	81	32.7		
(p.m.)		135	3.8	78	27.3		
12/16		127	4.7	83	20.6	7.4	

mitted to the Philadelphia General Hospital five years later (Feb. 2, 1955) because of epistaxis, lethargy, blurring of vision, and severe headaches secondary to her hypertension.

Physical examination on admission revealed an obese, lethargic Negro woman. The pulse was 100 per minute and regular; the respiratory rate was 24 per minute, and the blood pressure was 270/200. The eyegrounds showed Grade IV hypertensive retinopathy, attested by the presence of bilateral papilledema, exudates, and hemorrhages. The lungs were clear. There was a marked grade of cardiac enlargement; the rhythm was regular and a short, low-pitched, blowing Grade 2 systolic murmur was heard at the apex.

Laboratory studies on admission revealed a hemoglobin of 12.2 gm. per 100 ml. The BUN was 51 mg. per 100 ml.; this slowly increased, so that by March 19 it was 154 mg. per 100 ml.

Because of the patient's precarious state, she was treated with parental ganglionic blocking drugs and 50% magnesium sulfate. The urinary output gradually diminished to 100 ml. per day. By March 18, 1955, the patient had become comatose. On March 22, 1955, the electrocardiogram showed widened QRS complexes and absent P waves. The serum potassium had increased to 6.4 mEq. per liter. The blood pressure was 280/160. Because of the apparent potassium intoxication, 200 cc. of M. S. L. was infused in 15 minutes under electrocardiographic control. The ventricular rate increased from 40 to 49 per minute, and the P waves, previously undiscernible, became visible. These effects occurred toward the end of the infusion and were sustained only briefly after the infusion was discontinued. Significant findings before and after administration of sodium lactate are recorded in Table 4. Death occurred suddenly 12 hours later. Postmortem examination confirmed the clinical impression of malignant hypertension.

CASE 5.—An 85-year-old white woman was admitted to the Philadelphia General Hospital on May 6, 1955, with a history of rectal hemorrhage, increasing constipation, and marked loss of weight.

Examination revealed marked pallor, but the patient did not appear to be in any acute distress. The heart was enlarged to the left; a Grade 3 rasping systolic murmur was audible at the apex. The blood pressure was 120/50. The liver was palpable 2 fingerbreadths beneath the right costal margin. Occasional rales were heard at the right base. On the day of admission the hemoglobin was 7 gm. per 10 ml.; the BUN was 19 mg. per 100 ml. An upper gastrointestinal series and a barium enema were unrevealing, and sigmoidoscopy was negative. The BUN slowly rose to 149 mg. per 100 ml. by May 23. Thereafter, it ranged between 122 and 144 mg. per 100 ml. Other evidence of diminished renal function was indicated by a markedly reduced phenosulfonphthalein excretion and fixation of the specific gravity at 1:011. On June 7, 1955, because of an elevated serum potassium (7.5 mEq. per liter) with electrocardiographic changes, 150 cc. of M. S. L. was given in 10 minutes. At the end of the infusion the patient complained of substernal compression radiating up into the neck. The blood pressure, which had been 120/50 prior to therapy, dropped to 95/40 during the pain. A few coarse, moist rales were noted in each base. Morphine sulfate and oxygen by mask were given, with return of the blood pressure to 115/55 and relief of symptoms within 20 minutes. Following the above episode the patient revealed that she had experienced symptoms of left heart failure in the recent past; her last attack had occurred on the

TABLE 4.—*Blood Chemistry and Serum Electrolyte Findings in Case 4 on March 12, 1955*

	pH	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	Ca, Mg./100 Ml.	Lactic Acid, Mg./100 Ml.
Control (before lactate)	7.33	122	6.4	75	15	7.0	9.6
½ hr. (after infusion)	7.30	131	5.9	72	17.5	6.2	25.0

TABLE 5.—*Blood Chemistry and Serum Electrolyte Findings in Case 5*

Date	BUN, Mg./100 Ml.	Creatinine, Mg./100 Ml.	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	Ca, Mg./100 Ml.
7/7 Control	122	4.0	130	7.6	98.1	15.3	9.1
7/7 (20 min. later)		4.1	122	6.7	108.1	11.3	
7/15	144	3.5	129	5.2	100.1	11.3	8.9

night prior to administration of the sodium lactate. With continued supportive treatment the serum potassium slowly dropped to 5.2 mEq. per liter. The significant chemistry and electrolyte data are recorded in Table 5.

This patient gradually improved, and although still azotemic and mildly anemic with vague mental difficulties, she was able to be ambulatory and was discharged to a nursing home three months following hospitalization.

The final diagnosis was gastrointestinal hemorrhage of unknown etiology, uremia (probably secondary to chronic pylonephritis), and arteriosclerotic heart disease with cardiac enlargement.

CASE 6.—A 51-year-old Negro woman was admitted to the Hospital of the University of Pennsylvania on Feb. 24, 1956, complaining of a severe high midepigastric pain of 48 hours' duration. The history disclosed that the patient was a known hypertensive and a mild diabetic. The diabetes mellitus had been well controlled on diet and 20 units of isophane insulin injection (NPH insulin) daily. There was no history of cardiac decompensation or angina pectoris. The patient had been aware of a diminishing urinary output since December, 1955; during this time she had also become progressively lethargic and anorexic. For two days prior to hospitalization she experienced severe continuous parumbilical pain which extended high into the midepigastrium, went through to the back in the left infrascapular area, and extended up into the left side of the neck.

When seen in the receiving ward she was dyspneic, confused, and lethargic. The blood pressure was 140/80, and the pulse was 130/minute and regular. The ocular fundi showed a Grade II hypertensive retinopathy. Rales were present at the right base posteriorly. The heart was greatly enlarged to the left. A harsh Grade 2 aortic systolic murmur which extended into the neck and a blowing Grade 4 mitral systolic murmur were present. The liver edge was palpated 3 fingerbreadths beneath the right costal margin. There was no peripheral edema. The femoral pulses were strong and equal bilaterally.

Laboratory studies showed the hemoglobin to be 11.9 gm. per 100 ml. The white blood cell count was 15,200, with a polymorphonuclear leukocytosis. Urinalysis showed 2-3 WBC and 5-6 RBC per high-power field; a trace of albumin was present. On admission the blood sugar was 475 mg. per 100 ml., and the BUN was 140 mg. per 100 ml. An electrocardiogram taken before the results of the serum electrolytes became available showed widened QRS complexes measuring 0.18 second, absent P waves, and a ventricular tachycardia or a supraventricular tachycardia with aberration of the ventricular complexes. Coincident with the tachycardia the blood pressure fell to 100/50. One hundred milliequivalents of sodium lactate (40 cc. of 2.5 M) was given rapidly intravenously over a period of 30 seconds. A continuous electrocardiographic tracing during administration of the sodium lactate showed immediate QRS narrowing, and within several minutes normal sinus rhythm was restored with a rate of 88/minute (Fig. 4). The blood pressure rose to 140/90, and there was marked clinical improvement in the patient. Blood chemistry and serum electrolyte determinations were then performed, and the results are recorded in Table 6. The serum potassium was 7.6 mEq. per liter. Shortly thereafter the ventricular tachycardia recurred. Again this was treated with 100 mEq. per liter of 2.5 M sodium lactate intravenously, with restoration within several minutes to normal sinus rhythm. Over the next five days the patient remained in normal sinus rhythm. Treatment consisted of daily infusions of hypertonic dextrose and insulin, sodium lactate, and calcium

TABLE 6.—*Blood Chemistry and Serum Electrolyte Findings in Case 6*

Date	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	Ca, Mg./100 Ml.	BUN, Mg./100 Ml.	FBS,* Mg./100 Ml.
Admission							
2/23/56	131	7.6	95	11.3		140	475
2/23 (3 hr. after lactate)	130	6.3	93	21.4	8.6		
2/25	126	5.5	89	21.1	8.3	136	
2/28	136	4.2	93	22.7	8.0	156	92

* FBS=fasting blood sugar

gluconate, and gradually the patient became alert and oriented. Five days later she died of an apparently unrelated pulmonary embolism.

CASE 7.—A 24-year-old white woman was transferred to the Hospital of the University of Pennsylvania at 7:30 p. m. on May 19, 1956, for treatment of acute oliguria. The following history was obtained. The patient developed preeclampsia in the 32d week of an intrauterine pregnancy, and on May 15, 1956, she was admitted to another hospital with the diagnosis of abruptio placentae. Two hours following hospitalization she spontaneously delivered a stillborn infant and, following delivery of the placenta, passed a large clot. The estimated blood loss was 2000 cc. On the basis of additional hematologic studies, a diagnosis of hypofibrinogenemia was made. She then received 2000 cc. of whole blood intravenously. Subsequently she developed acute oliguria, the exact cause of which was uncertain. The transfused blood was retyped and cross matched and was said to be compatible. In spite of supportive therapy over the next few days, there was gradual clinical and chemical deterioration, and at 7:30 p. m., May 19, 1956, she was admitted to the University Hospital.

On examination the patient was semicomatose and in a shock-like state. The blood pressure was 100/60 and the heart sounds were distant and irregular. The lungs seemed clear on auscultation.

After blood had been drawn for the serum electrolyte and blood chemistry determinations, an electrocardiogram was taken (Fig. 5*A*). This showed paroxysms of ventricular flutter interspersed with even more bizarre beats. The serum potassium was found to be elevated to 10.7 mEq. per liter.

At 9:00 p. m. the patient was given 60 cc. of M. S. L. intravenously in about five minutes. There was some improvement in the configuration of the QRS complexes within 5 to 10 minutes. The sodium lactate was discontinued at 9:10 p. m., while the patient was given 50 cc. of 50% dextrose with 80 units of regular insulin intravenously. By 9:12 p. m. there was further deterioration of the electrocardiogram. During the next 11 minutes the patient was given an additional 10 mEq. of M. S. L. At 9:25 p. m. there was a marked change in the QRS complexes, which increased in amplitude and were narrowed. At 9:30 p. m. (Fig. 5*E*) there was an abrupt return of auricular activity and sinus rhythm. Coincident with a return to sinus rhythm there was immediate clinical improvement in the patient. The blood pressure increased to 160/110, and the patient became more responsive. The serum potassium level just before extracorporeal hemodialysis was 7.7 mEq. per liter. This represented a 3 mEq. change in the serum potassium concentration.

Because both M. S. L. and hypertonic dextrose with insulin were used in treating this patient, the 3 mEq. change in the serum potassium concentration (over a period of three hours) probably reflects the combined effects of therapy. The electrocardiographic and clinical improvement, however, occurred within a period of 10-15 minutes following the administration of M. S. L. This effect was similar to that observed in Cases 1, 2, 3, 8, 9, 10, and 11, where only M. S. L. was employed. The serum electrolyte and blood chemistry findings on admission (before dialysis) and after dialysis are recorded in Table 7.

The electrocardiogram taken on May 22, 1956, showed an essentially normal tracing. The patient continued to improve after artificial perfusion, and by June 1, 1956, had slowly entered the diuretic phase of her renal shutdown. During the next six weeks of her life a bleeding diathesis presented a major problem, and she died in mid-July, 1956, hemorrhaging from the nose, mouth, and rectum.

CASE 8.—A 59-year-old Negro woman was admitted to the Philadelphia General Hospital on July 30, 1956, in a semicomatose condition, with marked respiratory distress. She was immediately started on oxygen by mask and given morphine sulfate. No history was obtained at the time of admission.

Physical examination disclosed a blood pressure of 210/90 and a pulse of 110/minute, which was irregular. The patient was perspiring freely, yet her extremities were cool. A Grade 2 systolic murmur was heard over the entire precordium. There were moist rales in both lung bases and slight engorgement of the neck veins, but no

TABLE 7.—*Blood Chemistry and Serum Electrolyte Findings in Case 7*

Date	K, mEq./L.	Na, mEq./L.	Cl, mEq./L.	CO_2, mEq./L.	Ca, Mg./100 Ml.	P, Mg./100 Ml.	BUN, Mg./100 Ml.
Before dialysis							
Admission 5/19/56 8:00 p.m.	10.7	123	87	14.6			92
11:00 p.m.	7.7						
After dialysis 5/20/56	5.7	131	86	24.1	8.1	11.9	16

ankle edema. The patient's condition remained essentially unchanged for the next two hours, after which, however, the slightly irregular tachycardia increased to a rate of 140-150/minute and the blood pressure dropped to 150/90. An electrocardiogram was obtained at this time. Shortly thereafter respiratory distress increased and the blood pressure fell to 80 mm. systolic (no diastolic pressure was obtained); the pulse was 160 per minute and weak. This was followed, within minutes, by almost complete cessation of respirations (only gaspings at 4-5/minute). The pulse could no longer be felt; heart sounds were not audible on auscultation, and the eyes were staring, glassy, and areflexic. Respiratory gasps decreased to 2-3/minute. The patient then stopped breathing and apparently sustained a period of anoxia of about two to three minutes. In spite of this, artificial respiration was begun and M. S. L. was given into the right jugular vein at a rate of approximately 5 cc. per minute. Forty milliequivalents was administered, and the heart rate immediately became audible at 30-35 per minute. The sodium lactate was continued intravenously; after 75 cc. of M. S. L. the heart rate had increased to 80 per minute, the blood pressure slowly returned to near control values, and the patient breathed spontaneously. Subsequently, the heart rate gradually increased to 130 per minute. Frequent electrocardiograms were taken over the next 7½ hours (Fig. 6); the patient received a total of 425 cc. of molar sodium lactate. Her condition remained stable; she was markedly improved clinically, well oriented, and able to relate a history. Within 24 hours after treatment with M. S. L. a spontaneous diuresis (3000 cc.) occurred. At 8 a. m., July 31, 1956, M. S. L. was discontinued. The BUN on admission was 149 mg. per 100 ml.; serum electrolytes could not be determined because of hemolysis. On July 31, 1956, (the following morning) the BUN was 139 mg. per 100 ml.; serum Na, 147 mEq. per liter; K, 3.9 mEq. per liter; Cl, 105 mEq. per liter; CO_2 combining power, 61 vol.%. The hemoglobin was 6 gm. per 100 ml. In spite of a daily urinary output averaging 2000-3000 cc. and treatment with antibiotics, supportive fluids, and electrolytes, the patient remained markedly azotemic and died on Aug. 13, 1956. No postmortem examination was performed.

Case 9.—A 68-year-old Negro man was transferred from another institution to the Philadelphia General Hospital on June 12, 1956, because of pyuria and hematuria. On admission he was debilated and dehydrated and appeared both acutely and chronically ill. The chest was emphysematous; no rales were heard. The heart sounds were distant, and no murmurs were audible; the rhythm was regular at 120 per minute. The blood pressure was unobtainable, and no peripheral pulse could be detected. On auscultation, however, an irregular rhythm with a rate of 80 per minute was audible. An electrocardiogram was taken, and the diagnosis of advanced (Stage III) potassium intoxication was made. The patient was given 100 cc. of M. S. L. over a period of 15 minutes. Immediately after completion of the infusion there was restoration of the blood pressure to 130/90, an increase in the pulse rate and volume, and a striking improvement in the electrocardiogram, with a return to a relatively normal tracing and improvement in the skin color. The serum chemistry and electrolyte findings immediately before and 30 minutes after infusion of the sodium lactate are recorded in Table 8.

Clinical and electrocardiographic improvement was maintained for the next 48 hours. The patient was treated with sodium lactate, sodium chloride, dextrose and insulin, and antibiotics. In spite of these measures he gradually became more azotemic (BUN of 166 mg. per 100 ml.) and deteriorated clinically. His serum potassium on 6/19/56 was 5.3 mEq. per liter. On June 20, 1956, he died; a postmortem examination was performed. The final diagnosis was necrotizing pyelonephritis, uremia (with hyponatremia, azotemia, and acidosis), chronic cystitis, and postsuprapubic cystotomy.

Cases 10 and 11.—These cases have been reported in previous communications.[3,4]

Comment

The electrocardiographic patterns of hyperpotassemia have been fairly well documented.[1,2,5-7] In man the electrocardiographic effects are somewhat more complicated than in the experimental animal. In the human, death due to hyperpotassemia probably occurs at serum concentrations of from 8-12 mEq. per liter. Death usually results from ventricular standstill; rarely, from ventricular fibrillation. In the human, also, cardiotoxicity does not develop in a gradual manner with a stepwise increase in severity through Stages I, II, III, and IV, but may progress suddenly from Stage I to Stage III or IV.

Table 8.—*Blood Chemistry and Serum Electrolyte Findings in Case 8*

	K, mEq./L.	Na, mEq./L.	CO_2, mEq./L.
Before 100 mEq. molar sodium lactate	7.8	102	10
30 min. after molar sodium lactate	7.2	103	12

Although the electrocardiogram reflects the ratio of the intracellular to the extracellular potassium concentration, the hyperpotassemic effects are probably the result chiefly of the extracellular potassium, particularly that in the heart muscle. The characteristic electrocardiographic changes are therefore primarily dependent upon the serum potassium concentration; they are almost immediately reversed as the extracellular potassium falls. Even slight changes in the serum level are often associated with marked clinical and electrocardiographic improvement.

Factors Modifying Potassium Toxicity.—There is only a fair correlation between the serum potassium concentration and the extent of the electrocardiographic changes. Some patients often have marked electrocardiographic evidence of toxicity at relatively low serum levels. Sensitivity to potassium is increased (*a*) in patients in the older age group, particularly those with arteriosclerotic and coronary artery disease and those with recent myocardial infarction,[5,8] (*b*) in the presence of shock, (*c*) in patients with congestive heart failure, and (*d*) in the presence of low serum levels of sodium and calcium.[2,9]

Mechanism of Effect of M. S. L.—Molar sodium lactate decreases the extracellular potassium concentration by the following mechanisms:

(*a*) It causes expansion of the extracellular space—there is a relatively rapid increase in the extracellular fluid volume, with a consequent decrease in the potassium concentration.[10]

(*b*) The serum potassium tends to move intracellularly, thereby decreasing the total amount of extracellular potassium. This is probably the result of the increase in blood pH produced by M. S. L. and other factors to be discussed subsequently. With acidosis potassium tends to move out of the cell, and extracellular concentration of this cation is increased. The decrease in the acidosis resulting from the administration of M. S. L. not only arrests this shift of potassium but actually shifts it intracellularly. This has been shown experimentally in nephrectomized animals.[10,11] The data obtained in the experimental animal also suggest that the administration of M. S. L. raises the threshold for the development of toxic potassium effects. Following the administration of M. S. L. a serum level of 2 mEq. per liter or more above the control was required to produce similar degrees of toxicity, as noted by the electrocardiogram.[11]

(*c*) Experimental data indicate that the measured increase of extracellular lactate represents but a small fraction of the infused amount, suggesting an intracellular shift of the lactate.[10] It is possible that the lactate may also be a factor in the intracellular shift of potassium.

(*d*) The effect of the alkalosis, the sodium ion, and a vagolytic action have been previously reported.[2,3,12-20]

Rapidity of Action.—The effect of molar sodium lactate in the treatment of hyperpotassemia is apparent within a relatively short period of time: 1 or 2 minutes in the experimental animal[10,11] and 2 to 30 minutes in the human subject. (The ranges from extreme toxicity before treatment with M. S. L. to a more normal-appearing electrocardiogram following therapy are noted in Figures 1 to 3.) Because of its rapidity of action and its effectiveness in combating the altered physiology of hyperkalemia the use of this agent in the treatment of hyperpotassemia may be life-saving. The intravenous infusion reaches the heart first, and therefore the changes are probably more marked and occur earlier in this region than in the body as a whole, even though the electrocardiographic improvement usually parallels the reduction of the serum potassium level. Following the initial clinical improvement, time is then available to decide upon an additional and long-term therapeutic program—specifically attacking the cause of the hyperkalemia. Small doses of M. S. L. (depending on serum electrolyte, blood chemistry, and electrocardiographic find-

ings), if given daily over long intervals, may be sufficient to maintain adequately relatively normal serum potassium levels. Administration of oral molar sodium lactate may also suffice for this purpose. In many cases we have been able to correlate the electrocardiographic evidence of amelioration of the potassium intoxication with improvement in the clinical state and normalization of the blood pressure. In two instances (Cases 3 and 6), 2.5 M sodium lactate was used and appeared to have an added advantage in that the same beneficial effect was obtained with a smaller total fluid volume. Because of the associated hypocalcemia in some cases, administration of this electrolyte had an additional beneficial effect.

Toxic Effects.—We have observed two episodes of left heart failure (Cases 3 and 5) following the administration of sodium lactate. Since a reasonably large quantity of M.S.L. is often necessary to achieve reversal of the toxic potassium effects in patients with various grades of renal insufficiency, consideration should be given to the potential hazard of sodium excess and the possibility of the subsequent development of pulmonary edema in these patients.

Comparison of M. S. L. with Other Therapy.—Although many electrolyte solutions and other methods of therapy for hyperkalemia are available, the relative efficacy and indications for their use have not been clearly defined. Hypertonic sodium chloride (3% to 5%) has been used with some success, particularly in the presence of a low serum sodium, since sodium protects against toxic potassium effects. Although this solution decreases potassium concentration, it does so chiefly as the result of expansion of the extracellular fluid volume. The extracellular potassium either remains the same or actually increases.[11,21] Moreover, probably as a result of the chloride radical, there is often a further decrease in pH,[11] which tends to perpetuate the hyperkalemia.

Sodium bicarbonate has also been used with some success. Its action is qualitatively similar to that of M. S. L., since the alkalinizing effect of the latter solution depends on its sodium bicarbonate content.[22] We are at the present time attempting to compare the relative efficacy of these solutions in the experimental animal and in the human subject and to determine their relative indications in therapy. The experimental work in animals[11] suggests that the action of sodium bicarbonate is somewhat less effective and may be more toxic than M. S. L.

Calcium, a pharmacologic antagonist to potassium, has been used for some time in the therapy of hyperpotassemia.[23] It is particularly efficacious in the presence of a low serum calcium, which enhances the toxicity of potassium. Therefore, the restoration of a normal serum calcium level is of help in therapy. However, in the presence of a normal serum calcium in the control, the administration of calcium would significantly increase the serum level and might add another toxic factor. In the dog, with a normal serum calcium in the control, high serum levels (up to 20 mg., which is within the toxic range) were required to counteract the toxic effects of potassium.[11]

Hypertonic dextrose and insulin has been shown to be particularly valuable in therapy. Comparison of this method with M. S. L. is now in progress. Our tentative impression suggests that, while frequently efficacious, hypertonic dextrose and insulin are less often effective. In the more advanced grades of hyperpotassemia, particularly those associated with shock, hypertonic dextrose and insulin seldom significantly change either the serum potassium level or the clinical and electrocardiographic abnormalities. There is some evidence to suggest that while hypertonic dextrose and insulin will decrease the serum potassium, in the presence of normal circulatory dynamics, this decrease is often transient, and the degree of acidosis is often not materially

TABLE 9.—*Summary of Cases**

Case†	Age	Sex	Clinical Diagnosis	Pretreatment ECG, Grade of Potassium Intoxication	Amount Given	Time	ECG After Treatment	Clinical Effects	Ultimate Fate of Patient	Remarks
1	51	F	HCVD and uremia	Supraventricular tachy. (?); no P waves	160 cc.	30 min.	Restoration to sinus rhythm and narrowing of QRS complexes	Increase in BP from shock to normal levels clinically improved	Died 17 days after treatment	Died of unrelated pulmonary embolism
2	63	M	Acute & chronic alcoholism with liver and renal damage & gastroenterocolitis	STAGE III	300 cc.	7 min.	Restoration as above	Marked clinical improvement	Lived & was discharged from the hospital	Administration of M.S.L. was lifesaving
3	61	M	Chronic lymphatic leukemia; renal calculi	STAGE IV	225 cc.	10-15 min.	Within several minutes restoration to normal sinus rhythm & narrowing of QRS complexes	Marked clinical improvement; no effect on BP	Died 5 days after treatment	Developed pulmonary edema after treatment
4	19	F	Malignant hypertension	STAGE III	200 cc.	15 min.	Within 10 min. incr. in ventric. rate & return of auricular activity	None anticipated	Died 12 hr. after treatment	Terminal on admission
5	85	F	ASCVD, uremia	STAGE I	150 cc.	10 min.	ST segment depression which was transient	Substernal pain; fall in BP; pulmonary congestion	Lived and was discharged from the hospital	Developed untoward effects immediately following administration
6	51	F	Diabetes mellitus & uremia	STAGE III	100 cc.	2 min.	Immediate QRS narrowing and return to sinus rhythm	Marked clinical improvement	Died 5 days later of unknown cause	Terminal on admission
7	24	F	Hypofibrinogenemia; postpartum hemorrhage and blood transfusion reaction	STAGE IV	160 cc.	15 min.	As above	Patient more alert; blood pressure increased from 100/60 to 160/110	Died 30 days later of uncontrolled hemorrhage and uremia	Administration resulted in immediate clinical & ECG improvement & allowed patient to undergo hemodialysis; kidneys were irreversibly damaged
8	56	F	Uremia & HCVD	STAGE III to STAGE IV	425 cc.	8 hr.	Gradual narrowing of QRS complexes and return to normal sinus rhythm	Patient alert; BP increased to 200/100	Died 14 days after treatment of unknown cause	Administration of M.S.L. was temporarily lifesaving for this patient
9	68	M	Uremia	STAGE III	100 cc.	15 min.	Normalization	Restoration of BP from shock levels; improvement in skin color	Died 8 days after treatment	No permanent improvement anticipated
10	59	M	Rheumatic H. dis. with aortic stenosis & aortic insufficiency; LVH; uremia	STAGE III to IV	300 cc. M.S.L.; 600 cc. 2.5 M sodium lactate	5 hr. 30 min.	As above	BP increased from shock levels to 140/95; became alert and oriented	Died 30 hr. after treatment	Died of pulmonary embolism
11	58	M	Postop. shock & hemorrhage; acute oliguria	STAGE IV	740 cc.	4 hr. 40 min.	Normalization; narrowing QRS & return sinus rhythm	Marked clinical improvement; elevation of BP from 90/40 to 140/80	Died 18 hr. after treatment	Died as result of unknown cause

* M.S.L. indicates molar sodium lactate; HCVD, hypertensive cardiovascular disease; ASCVD, arteriosclerotic cardiovascular disease; BP, blood pressure.
Cases 10 and 11 have been previously reported.[9,4]

affected [11]; the tendency is, therefore, for the potassium to shift extracellularly within a short time. On the other hand, M. S. L. has been used successfully in 11 consecutive cases (Table 9). In one of these patients (Case 7) M. S. L. and hypertonic dextrose with insulin were employed together.

The use of molar sodium lactate is not intended to replace the artificial kidney where indications for its use are present. However, this preparation may be used when no artificial kidney is available and in the acute case of severe potassium poisoning in order to allow the time necessary for setting up the artificial kidney (Case 7).

Summary

In hyperpotassemia death occurs primarily from its cardiotoxic effects. There is a marked similarity between the terminal cardiac mechanisms and those observed in hyperkalemia. Because of the improvement of the former by molar sodium lactate (M. S. L.) and because of the rapid effect of this solution in lowering the extracellular potassium, it was felt that M. S. L. might be efficacious in treating this abnormal state.

Eleven patients with advanced cardiotoxic manifestations were treated with M. S. L. Many of these patients were moribund, with an unobtainable blood pressure. The electrocardiograms showed a slow, irregular rhythm with widened ventricular complexes, and in some cases the complexes resembled those of ventricular flutter. In general, most of these subjects had the chemical and electrolyte patterns observed in uremia. The electrocardiograms resembled the terminal tracings of the dying heart. Marked improvement was observed within 5 to 30 minutes after the intravenous administration of M. S. L., depending on the dose and speed of administration. The blood pressure returned to a more normal value, and there was general improvement in the clinical state of the patient. Coincidentally, the electrocardiograms showed a return of the bizarre QRS complexes to a normal or a relatively normal configuration. The serum potassium values in the 11 patients before treatment ranged from 7.5 to 10.8 mEq. per liter.

The dose of sodium lactate ranged from 100 to 350 mEq., administered intravenously over a period of from five minutes to three hours.

Toxic effects consisted of the development of pulmonary edema in two patients.

In most of the patients, reversal of the toxic cardiac effects was of considerable benefit; often, however, the underlying renal damage was of such severity that it was incompatible with life. As a result, five patients died within 7 days after treatment with M. S. L.; four additional patients died within 8 to 30 days following treatment, and two patients survived and were discharged from the hospital.

M. S. L. was found clinically and experimentally to be superior in many respects to the other measures commonly employed: i. e., sodium chloride, calcium, sodium bicarbonate, and hypertonic dextrose with insulin.

It is felt that the use of M. S. L. is an important adjunct in the treatment of hyperpotassemia. Its rapidity of action and ease of administration give this preparation a high priority in the therapy of this state.

2021 Spruce St.

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Clinical and Laboratory Observations on Chlorothiazide (Diuril)

An Orally Effective Nonmercurial Diuretic Agent

RALPH V. FORD, M.D.; JOHN H. MOYER, M.D., and CHARLES L. SPURR, M.D., Houston, Texas
With the Technical Assistance of Ann Alexander, Carol Marsh, and Jean Gaffney

Chlorothiazide * is a compound whose properties make it valuable in cases where it is desirable to increase the elimination of sodium, chloride, and water. It is a nonmercurial orally active compound [1] which produces a broad spectrum of electrolyte excretion effects and a diuretic effect equal to or greater than that seen following the administration of currently available oral diuretics.

This report presents data on the compound concerning its effect in man and the laboratory dog on the excretion of water and electrolytes, the relationship of dosage to the increase in sodium excretion, the onset and duration of its action after oral and parenteral administration, its clinical efficacy, and the comparative potency as a diuretic agent as compared to various diuretics which are already available.

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From the Departments of Medicine and Pharmacology, Baylor University College of Medicine, and the Veterans' Administration Hospital.

Currently Professor of Medicine, The Hahnemann Medical College and Hospital, Philadelphia (Dr. Moyer); Professor of Medicine, Bowman Gray School of Medicine, Winston Salem, N. C. (Dr. Spurr).

* 6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide, supplied by Research Laboratories, Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. To be commercially available as Diuril.

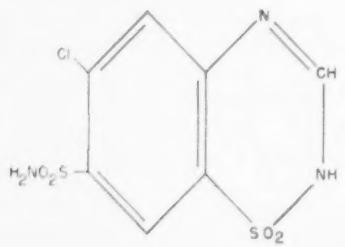


Fig. 1.—Structural formula for chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiazine-1,1-dioxide).

Methods and Materials

A. Laboratory Observations.—The acute diuretic response to chlorothiazide was observed in 34 dogs. Thirty-two studies were done using unhydrated dogs (Group I), and 16 studies were done using dogs (Group II) which were hydrated with 35 cc. per kilogram of body weight of water one hour prior to the study. Concurrent renal function studies were done on the dogs in Group II. The dogs in Group I were taken from their cages on the morning of the study, anesthetized with 30 mg. per kilogram of pentobarbital, and then catheterized. Control observations were made using three 20-minute urine collection priods. Then the chlorothiazide was given intravenously, employing 0.5, 1, 2, and 10 mg. per kilogram of body weight of the drug. Eight dogs were studied at any one time, the size of the initial dose being randomized among them. In subsequent studies the dose was rotated among the dogs in such a fashion that each of the four doses was administered eight times. When a dog was used more than one time, one week was allowed between studies in order to allow for restabilization of water and electrolyte excretion. After the drug was administered, urine was collected for four hours, employing successive 20-minute collection periods (Table 1). Urine volume was determined, and the excretion rates of sodium, potassium, and chloride were determined for each animal, employing methods and techniques as previously described.[2]

Observations were made on water and electrolyte excretion on 16 dogs in Group II during concurrent renal function studies. The methods and techniques have been described previously.[3] Following control observations using three 10-minute urine collection

periods, the dogs were given the chlorothiazide intravenously at two dose levels, i. e., 0.5 mg. and 10 mg. per kilogram. Following the drug administration, observations were made over a three-hour period, employing successive 10-minute urine collection periods (Tables 2 and 3).

B. Clinical Observations.—The subjects of this study were 10 men who had previously presented congestive heart failure which at the time of the study was compensated, presenting no detectable edema. They were maintained, as described previously,[4] on the metabolic ward, where they were ambulatory and were fed a diet containing 50 mEq. of sodium and 3000 ml. of purified (distilled) water, U. S. P., daily. The diet was otherwise constant with respect to carbohydrate, protein, and fat, as well as Calories. The initial observations consisted of administering orally in single dosages 31, 62, 125, 250, 500, 1000, 2000, and 4000 mg. at 6 a. m. on the day of the study to determine the sodium excretory response range as part of a pilot study. When the characteristics of the sodium response curve were determined, it became apparent that the effective dose lay between 1000 and 2000 mg. In the control state and during the administration of all the dosages in the pilot study, observations were made of the urinary excretion products in six periods per 24 hours—three consecutive two-hour periods and three consecutive six-hour periods. These included the excretion rates of sodium and potassium (Beckman flame photometer [direct-reader]), ammonia,† chloride,‡ bicarbonate,§ titratable acidity (Beckman automatic titrater), total solutes (Beckman osmometer [freezing point depression]), and, in a few instances, phosphate.‖ The pH of each period was also determined (Beckman pH meter, Model G).

After the pilot study indicated that the dose range for effective diuresis lay between 1000 and 2000 mg., 10 observations on the 24-hour excretion rate of sodium were made at each dose and the data (increase in sodium excretion on the day of the drug over the control day) subjected to an analysis of variance. This analysis compares the dosage-response curve of chlorothiazide with that of a standard diuretic (Mersoben¶), according to techniques previously described.[4] These data can then be used to determine the "potency estimation" of chlorothiazide compared to Mersoben, as well as to other diuretics (meralluride,‖ chlormerodrin,# etc.).

In order to gain additional pharmacologic information, one nonedematous patient, eating a diet containing 50 mEq. of sodium, was given 2000 mg. of chlorothiazide at 6 a.m. for five consecutive days, and the total electrolyte excretion pattern was observed as in the pilot study. Since there was a decline in the natriuretic effect on the fourth and fifth days, another nonedematous patient, eating a diet containing 150 mEq. of sodium, was given 2000 mg. of the drug daily for five consecutive days to determine renal tolerance to the drug. Another edematous person, who had heart failure and who had been given a low-sodium diet (35 mEq. per day) for several years was observed for daily weight loss when given 500 mg. of the drug twice daily. One patient was given the drug at a dose of 1000 mg. at 6 a. m. and 6 p. m. on one day to compare the increase in sodium excretion obtained after giving the drug twice daily with that obtained after a single dose. Another patient was given a dose of 2000 mg. intravenously over a 60-minute period and the increase in sodium excretion compared with that obtained after the same dose was given orally. In order to determine differences in potassium excretion on repeated administration within a 24-hour period, one patient was given 4000 mg. of the drug once, at 6 a. m., and after a suitable recovery period was given 1000 mg. every 6 hours for four doses within a 24-hour period. The patterns of sodium and potassium excretion were then compared. To determine clinical efficacy and toxicity, 20 patients have been given daily doses varying from 250 to 2000 mg. for a three-month period as part of the outpatient management of chronic congestive heart failure.

Results

A. Laboratory Observations.—The effect of chlorothiazide when administered to unhydrated dogs is summarized in Table 1. There was a marked increase in sodium ($P<0.001$) and chloride excretion ($P<0.05$) and a moderate increase in water ($P<0.001$) and potassium excretion ($P<0.01$). This effect persisted throughout the four-hour period of observation following drug administration. The effect on water

† Folin and Bell Permutit (exchange silicate) method (Hawk, Oser, and Summerson,[7] p. 830).

‡ Sendroy modification by Van Slyke and Hiller (Hawk, Oser, and Summerson,[7] p. 895).

§ Van Slyke method (Peters and Van Slyke,[8] p. 290).

‖ Fiske and Subbarow method (Hawk, Oser, and Summerson,[7] p. 889).

¶ Su-1775 (Ciba Pharmaceutical Products, Inc.), parenteral mercurial diuretic; 1-S(5,6-bis-[1,2-dihydroxyethyl]-2-*p*-doranylmethyl-mercuri)-1-thiosorbital.

‖ Mercuhydrin (Lakeside Laboratories, Inc.), parenteral mercurial diuretics.

Neohydrin (Lakeside Laboratories, Inc.), oral mercurial diuretic.

TABLE 1.—*Effect of Chlorothiazide on Water and Electrolyte Excretion in Unhydrated Dogs (Group I)**

Dog No.	Urine Volume, Cc./Min.							Urine Sodium, μEq/Min.							Urine Potassium, μEq/Min.							Chloride, μEq/Min.							Dog Wt., Kg.
	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	C	D_1	D_2	D_3	D_4	D_5	D_6	
Subgroup 1A—10 mg./kg. of chlorothiazide given intravenously																												
1	0.2	0.9	0.8	0.3	0.5	0.8	0.7	4	100	95	29	41	70	58	5	27	42	31	14	12	10								8.0
2	0.3	1.1	1.1	0.7	0.7	0.6	0.4	5	130	170	128	90	79	50	8	49	36	34	26	19	19								13.0
3	0.2	0.7	1.1	0.7	0.8	0.6	0.3	19	143	215	143	143	97	61	7	12	17	10	31	23	17								13.0
4	0.2	0.9	0.9	0.6	0.4	0.3	..	2	155	175	120	143	61	..	6	49	41	26	16	16	..	1	49	79	51	77	43	..	14.0
5	0.1	1.0	1.0	0.8	0.2	0.1	0.2	11	180	190	130	20	13	20	8	7	9	9	4	2	2	8	137	145	96	23	7	12	12.0
6	0.5	2.4	1.8	1.4	0.8	0.6	0.5	24	510	390	308	170	110	53	7	63	47	28	11	13	9	4	407	311	253	165	134	60	13.0
7	0.1	1.3	0.9	0.8	0.7	0.4	0.4	10	225	175	153	115	73	48	6	33	20	16	11	12	10	5	132	111	122	116	71	61	13.0
8	0.1	0.9	0.8	0.7	0.3	0.3	0.3	6	120	150	160	50	70	53	3	43	30	23	14	15	16	1	69	42	83	47	29	28	13.0
Mean	0.2	1.2	1.1	0.8	0.6	0.5	0.4	10	196	195	146	97	72	49	6	35	30	22	16	14	12	4	159	138	121	86	57	40	12.4
% of control	600	550	400	300	250	300			1,960	1,950	1,460	970	720	490		583	500	367	267	233	200		3,975	3,450	3,025	2,150	1,425	1,000	
P value†<	0.001	0.001	0.001	0.01	0.01	0.05			0.001	0.001	0.01	0.01	0.001	0.001		0.01	0.01	0.01	0.05	0.05	0.10		0.10	0.05	0.05	0.05	0.05	0.05	
Subgroup 1B—2 mg./kg. of chlorothiazide given intravenously																												
1	0.1	0.6	0.5	0.4	0.3	0.3	0.2	7	95	105	88	54	34	27	4	37	21	15	14	14	10	1	38	28	23	3	3	1	11.0
2	0.2	0.6	0.6	0.7	0.6	0.2	0.1	6	65	65	130	93	20	3	9	29	35	23	23	5	3	..	..	..	..	..	..	..	13.0
3	0.1	0.5	0.6	0.4	0.3	0.3	0.2	7	90	125	93	53	37	30	4	14	14	7	10	12	10	1	59	74	57	37	30	17	8.0
4	0.1	0.6	0.7	0.4	0.4	0.4	0.3	3	90	90	70	85	70	50	5	39	48	33	25	35	21	1	52	64	44	51	59	27	9.0
5	0.2	0.4	0.4	0.3	0.2	0.2	0.2	10	50	60	37	22	12	20	7	13	13	15	5	5	4	6	18	100	76	13	22	5	10.0
6	0.1	0.6	0.4	0.4	0.1	0.1	0.1	4	150	60	85	90	6	14	2	13	5	10	2	4	8	5	61	34	50	13	3	2	8.0
7	0.2	0.5	0.4	0.4	0.4	0.2	0.2	8	90	75	65	55	25	22	6	22	14	20	28	16	9	..	..	..	..	..	..	..	10.0
8	0.2	0.8	0.6	0.4	0.3	0.2	0.2	15	120	100	75	40	38	23	11	56	43	31	13	12	13	7	99	74	54	14	9	10	11.0
Mean	0.2	0.6	0.5	0.4	0.3	0.2	0.2	8	94	85	80	62	30	24	6	28	24	19	15	13	10	4	55	62	51	22	21	10	10.0
% of control	300	250	200	150	100	100			1,175	1,063	1,000	775	375	300		467	400	317	250	217	167		1,375	1,550	1,275	550	525	250	
P value†<	0.001	0.001	0.001	0.01	0.10	0.50			0.001	0.001	0.001	0.01	0.05	0.05		0.01	0.01	0.01	0.05	0.20	0.20		0.01	0.01	0.001	0.10	0.20	0.20	
Subgroup 1C—1 mg./kg. of chlorothiazide given intravenously																												
1	0.2	0.4	0.4	0.3	0.2	0.2	0.2	13	70	75	62	47	24	17	3	10	9	7	6	5	4	4	39	37	36	29	20	9	11.0
2	0.3	0.5	0.4	0.4	0.3	0.3	0.2	20	85	85	75	45	38	24	7	9	6	5	6	9	6	24	27	47	50	32	31	12	13.0
3	0.2	1.4	1.1	0.8	1.0	1.7	0.6	30	305	315	207	137	68	73	13	46	33	17	19	10	7	19	196	212	213	141	33	15	14.0
4	0.3	1.2	1.2	1.6	1.5	1.4	1.0	33	250	225	225	155	120	120	8	38	36	33	41	37	32	6	127	150	140	109	79	55	17.0
5	0.2	0.2	0.2	0.5	0.3	0.3	0.3	2	125	153	123	77	69	68	6	13	13	12	10	11	7	5	85	19	21	27	20	24	13.0
6	0.3	0.8	0.6	0.5	0.4	0.3	0.3	3	75	60	70	58	38	25	10	59	48	35	20	20	21	1	100	70	62	41	22	14	17.0
7	0.2	0.3	0.3	0.2	0.2	0.2	0.1	3	13	26	30	13	3	8	5	16	12	10	9	8	11	2	16	26	27	11	3	3	11.0
8	0.4	0.7	0.6	0.5	0.3	0.3	0.3	5	35	35	30	10	10	15	3	3	3	5	4	6	6	5	85	19	21	26	20	24	6.0
Mean	0.3	0.7	0.6	0.6	0.5	0.6	0.4	14	120	122	103	68	46	44	7	24	20	16	14	13	12	8	84	73	71	52	29	20	12.8
% of control	233	200	200	167	200	133			857	871	736	486	329	314		343	286	229	200	186	171		1,050	913	888	650	363	250	
P value†<	0.05	0.10	0.10	0.20	0.30	0.40			0.05	0.05	0.01	0.05	0.05	0.05		0.05	0.05	0.05	0.10	0.20	0.20		0.01	0.05	0.05	0.05	0.05	0.20	
Subgroup 1D—0.5 mg./kg. of chlorothiazide given intravenously																												
1	0.2	0.3	0.3	0.2	0.2	0.2	0.1	13	50	40	40	19	12	8	3	10	6	6	2	5	6	1	38	28	23	3	3	1	10.0
2	0.2	0.4	0.2	0.2	0.2	0.2	0.1	2	20	10	10	3	4	3	2	2	6	4	2	1	1	..	..	..	..	..	..	..	8.0
3	0.2	0.5	0.7	0.4	0.3	0.2	0.2	23	70	125	83	70	55	38	12	25	40	23	13	7	8	4	49	88	44	26	11	5	12.0
4	0.2	0.5	0.4	0.3	0.2	0.2	0.2	2	50	40	15	4	3	4	11	39	36	14	8	10	11	2	33	31	14	4	3	4	10.0
5	0.1	0.3	0.2	0.2	0.1	0.1	0.1	4	27	29	32	6	4	4	7	65	43	27	9	18	9	3	8	6	8	3	2	2	10.0
6	0.2	0.6	0.5	0.6	0.5	0.3	0.3	22	180	135	108	90	55	60	9	20	15	11	35	19	28	5	68	64	46	18	3	1	8.0
7	0.1	0.5	0.4	0.3	0.2	0.2	0.2	10	50	30	25	19	9	15	3	29	17	8	9	7	14	1	55	38	38	16	4	6	11.0
8	0.2	0.4	0.4	0.3	0.2	0.2	0.2	9	72	91	65	22	19	12	6	6	3	3	9	5	8	4	54	53	45	25	16	10	10.0

| | | |

TABLE 2.—*Renal Hemodynamic Response to Chlorothiazide (Group II)**

Dog No.	Mean Blood Pressure, Mm. Hg					Glomerular Filtration Rate, Cc./Min.					Renal Blood Flow, Cc./Min.					Hematocrit					Dog Wt., Kg.
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	
Subgroup 2A—0.5 mg./kg. of chlorothiazide given intravenously																					
1	117	129	130	136	128	50	47	59	56	61	296	366	309	219	254	44	47	45	42	44	12.0
2	101	89	93	119	118	39	36	40	37	46	213	295	227	152	179	40	40	41	39	39	11.0
3	117	116	112	113	122	46	44	41	38	38	200	239	334	238	298	48	51	53	48	51	12.0
4	107	110	120	105	109	45	43	44	43	51	188	182	184	130	148	41	40	38	40	42	15.0
5	105	111	82	81	115	34	41	35	31	28	165	190	183	120	123	38	38	37	36	34	12.0
6	120	120	95	115	..	40	41	35	30	..	225	193	161	129	..	45	43	43	48	..	10.0
7	121	127	136	141	141	38	31	30	29	26	181	170	115	120	98	43	40	40	40	42	12.0
8	104	114	124	112	120	27	29	33	29	32	122	97	148	122	126	45	42	37	36	34	12.0
Mean	112	115	112	115	122	40	39	40	37	40	199	217	208	154	175	43	43	42	41	41	12.0
% of control		103	100	103	109		98	100	93	100		109	105	77	88		100	98	95	95	
P value<		0.30	0.50	0.50	0.01		0.50	0.50	0.20	0.50		0.30	0.50	0.05	0.50		0.50	0.50	0.20	0.30	
Subgroup 2B—10 mg./kg. of chlorothiazide given intravenously																					
1	110	128	106	111	131	37	33	35	35	36	226	226	254	181	152	34	38	37	37	37	11.0
2	122	125	107	130	134	41	30	37	35	32	212	180	202	171	151	40	45	45	49	43	13.0
3	148	133	135	130	149	27	32	29	29	30	222	291	202	161	185	50	53	50	46	48	9.0
4	120	117	100	118	130	37	29	37	36	40	202	130	217	166	192	40	47	37	39	39	12.0
5	128	119	120	137	140	24	22	21	22	26	154	159	140	109	113	44	46	48	45	45	11.0
6	110	106	105	110	113	36	34	37	39	41	130	119	158	154	202	29	30	38	35	40	10.0
7	122	120	137	141	138	42	33	39	37	40	168	121	159	143	147	41	39	41	44	42	11.0
8	95	86	103	99	90	35	30	31	30	37	202	170	158	130	163	50	50	50	50	48	9.0
Mean	119	117	114	122	128	35	30	33	33	35	190	175	186	152	163	41	44	43	43	43	10.8
% of control		98	96	103	108		86	94	94	100		92	98	80	86		107	105	105	105	
P value<		0.50	0.40	0.50	0.05		0.05	0.05	0.05	0.50		0.40	0.50	0.01	0.20		0.10	0.20	0.30	0.30	

* C, control observations—average of three 10-min. periods.
D_1, observations immediately after drug administration—average of two 10-min. periods.
D_2, observations 1 hr. after drug administration—average of two 10-min. periods.
D_3, observations 2 hr. after drug administration—average of two 10-min. periods.
D_4, observations 3 hr. after drug administration—average of two 10-min. periods.

TABLE 3.—*Effect of Chlorothiazide on Water and Electrolyte Excretion in Hydrated Dogs* (Group II)*

Dog No.	Urine Vol. Cc./Min.					Sodium Excretion, μEq./Min.					Potassium Excretion, μEq./Min.					Plasma Sodium, mEq./L.					Plasma Potassium, mEq./L.				
	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4	C	D_1	D_2	D_3	D_4
Subgroup 2A—0.5 mg./kg. of chlorothiazide given intravenously																									
1	1.0	2.4	5.5	4.0	4.1	96	292	276	168	316	32	42	52	60	78	144	144	147	146	153	3.7	3.9	3.9	3.9	4.3
2	0.5	1.6	1.3	1.6	1.6	17	204	48	16	76	13	42	25	25	48	137	137	140	139	139	2.6	2.5	3.1	2.5	3.0
3	0.4	1.0	1.9	1.7	2.0	9	88	69	36	36	29	32	32	28	26	149	153	150	153	153	2.5	3.1	3.1	3.9	4.0
4	0.5	1.6	2.1	1.2	1.1	17	146	172	62	64	20	52	42	33	35	142	145	149	151	153	2.4	2.2	2.5	2.5	2.5
5	0.4	1.8	1.7	1.1	1.4	13	262	94	26	24	16	49	42	19	30	135	139	137	140	139	2.3	2.7	3.1	3.3	3.3
6	0.8	2.4	1.5	1.2	...	55	316	74	42	...	17	33	21	18	...	134	139	139	142	...	3.4	3.2	2.8	3.2	...
7	0.9	2.4	2.5	2.9	2.4	31	176	78	95	70	19	38	22	22	30	142	140	142	148	150	3.2	2.4	2.8	3.4	3.6
8	0.5	1.0	1.1	0 8	1.2	23	82	58	72	92	14	24	32	33	52	133	133	132	132	130	4.0	3.8	3.9	3.5	4.0
Mean	0.6	1.8	2.2	1.8	2.0	33	196	109	65	97	20	39	34	30	43	140	141	142	144	145	3.0	3.0	3.2	3.3	3.5
% of control		300	367	300	333		594	330	197	294		195	170	150	215		101	101	103	104		100	107	110	117
P value		0.001	0.01	0.01	0.01		0.001	0.01	0.05	0.05		0.01	0.01	0.05	0.05		0.10	0.05	0.05	0.05		0.50	0.50	0.30	0.05
Subgroup 2B—10 mg./kg. of chlorothiazide given intravenously																									
1	0.8	2.9	3.5	3.2	3.0	77	328	348	254	204	9	57	52	31	33	128	130	135	135	137	3.5	3.8	3.3	3.1	3.7
2	0.4	1.6	1.8	1.3	1.9	48	200	220	137	176	13	50	58	30	35	142	142	140	143	144	3.1	3.1	3.7	3.4	3.5
3	0.4	1.9	1.2	2.4	2.2	39	214	116	128	104	5	38	20	23	38	141	145	152	158	158	2.8	2.8	3.0	3.2	3.5
4	0.4	0.5	1.9	1.5	2.8	16	16	228	152	158	9	22	57	33	60	138	138	138	142	144	3.2	2.6	2.6	2.8	3.1
5	0.5	2.1	1.1	1.2	1.1	44	354	262	142	130	7	39	31	16	23	136	137	140	136	136	3.3	3.3	3.5	3.7	4.0
6	0.8	2.7	1.8	1.6	1.8	9	232	152	142	194	11	33	42	44	38	132	136	134	134	138	3.4	3.3	3.4	3.0	3.2
7	0.7	2.3	2.9	2.8	2.7	21	184	164	146	184	9	38	39	26	42	140	128	138	140	145	3.8	2.1	4.3	4.1	4.2
8	1.9	3.0	3.0	2.1	2.3	65	206	212	166	234	21	42	42	34	33	136	138	143	148	150	3.2	3.4	3.1	3.4	4.0
Mean	0.7	2.1	2.2	2.0	2.2	40	217	213	158	173	11	40	43	30	38	137	137	140	142	144	3.3	3.2	3.4	3.3	3.7
% of control		300	314	286	314		543	533	395	433		364	391	273	345		100	102	104	105		97	103	100	112
P value <		0.001	0.001	0.01	0.001		0.001	0.001	0.001	0.001		0.001	0.001	0.001	0.001		0.50	0.20	0.05	0.05		0.50	0.50	0.50	0.05

* These are on the same dogs on which renal function studies were done (Table 2).

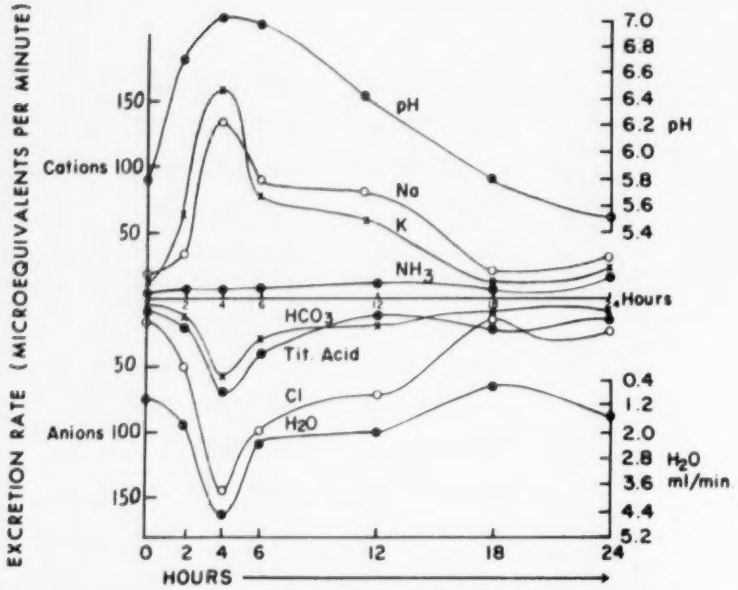
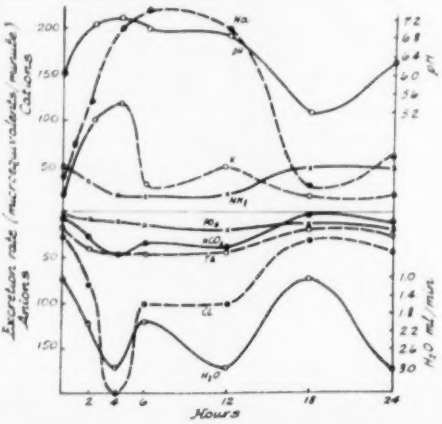


Fig. 2.—Electrolyte excretion patterns following 500 mg. of chlorothiazide given orally. The greatest responses are observed in the excretion of sodium and chloride accompanied by an alkaline urine. The rate of bicarbonate excretion is increased, but the total excretion is small. There is a prompt onset and short duration of action. Phosphate excretion is not altered.

per kilogram ($P<0.01$) and the 10 mg. per kilogram ($P<0.05$) dose. Glomerular filtration rate was not affected by a dose of 0.5 mg. per kilogram, but after the 10 mg. per kilogram dose it was slightly depressed ($P<0.05$), probably a response to the water and sodium loss associated with the diuresis. Renal blood flow was slightly depressed after a two-hour period in both groups, but only at the two-hour period was this response significant ($P<0.05$). The renal blood flow response may be related in part to the prolonged period of anesthesia rather than to any drug effect, since a similar reduction in renal blood flow is frequently observed in anesthetized animals which have not received any other drugs. It is not likely that chlorothiazide inhibits the renal tubular extraction of *p*-aminohippurate, since *p*-aminohippurate clearance was not reduced at the time that chlorothiazide exhibited its maximum effect. In conclusion, the diuretic response to chlorothiazide cannot be attributed to an increase in glomerular filtration rate, indicating that the diuretic response results from blockade of water and electrolyte reabsorption in the renal tubules.

The effect on water and electrolyte excretion in the hydrated dogs in Group II ap-

Fig. 3.—Electrolyte excretion patterns following 2000 mg. of chlorothiazide given orally. The greatest responses are observed in the excretion of sodium and chloride accompanied by an alkaline urine. The rate of bicarbonate excretion is increased, but the total excretion is small. There is a prompt onset and short duration of action. Phosphate excretion is not altered.



peared to be approximately the same as in the unhydrated animals in Group I. There was no evidence that plasma potassium and sodium were depressed. In fact, there was a slight over-all increase in the plasma concentrations of these electrolytes.

B. Clinical Pharmacology.—I. Electrolyte Excretion Patterns: The data presented graphically in Figures 2 and 3 indicate the excretion rates for the various moieties expressed as microequivalents per minute (sodium, potassium, ammonia, bicarbonate, titratable acidity, chloride, and phosphate) as milliliters of water per minute, as microosmols per minute of total solutes, or as pH. The greatest responses were seen during the second 2-hour period following the oral administration of the drug, with persistence of the response at a lower level for at least 12 hours and return to control levels during the third 6-hour period (18 hours after the drug). The response was characterized by an increase in all moieties observed, with the exception of ammonia, which showed a com-

TABLE 4.—*Timed Dosage Responses to Increasing Amounts of Chlorothiazide Administered Orally*

Moiety	Periods, Hr.	Low Dosage, 31-250 Mg.*		Middle Dose, 500-1,000 Mg.*		High Dose 2,000 Mg.*	
		Control	Drug	Control	Drug	Control	Drug
Sodium excretion, μEq/min.	2	30	61	18	81	10	120
	4	20	93	20	102	10	202
	6	33	79	23	111	25	211
	12	30	38	23	70	40	145
	18	27	60	33	43	31	30
	24	42	47	39	51	41	60
Potassium excretion, μEq/min.	2	30	59	35	62	10	102
	4	40	76	33	80	31	124
	6	60	71	40	71	32	44
	12	50	72	33	62	32	40
	18	30	50	35	32	10	20
	24	38	26	23	21	20	30
Ammonia excretion, μEq/min.	2	20	10	15	23	31	30
	4	20	11	33	10	81	21
	6	20	12	16	11	40	23
	12	10	10	20	13	41	22
	18	10	31	16	17	62	50
	24	10	31	15	22	30	30
Chloride excretion, μEq/min.	2	40	64	37	92	10	80
	4	50	69	35	71	22	201
	6	43	66	47	98	31	111
	12	23	31	47	61	31	71
	18	13	41	34	40	31	32
	24	23	28	34	42	22	30
Bicarbonate excretion, μEq/min.	2	2	20	4	9	1	28
	4	1	20	5	23	1	47
	6	3	22	9	13	2	23
	12	5	10	6	8	4	22
	18	8	12	3	2	2	1
	24	10	10	2	2	7	4
Titratable acidity excretion, μEq/min.	2	19	8	13	48	20	26
	4	16	55	11	46	10	48
	6	20	48	13	35	22	39
	12	20	3	9	17	27	35
	18	19	4	6	9	22	16
	24	19	7	7	3	21	20
Phosphate excretion, μEq/min.	2	11	13	11	11	2	7
	4	14	19	7	21	8	9
	6	19	24	13	11	11	13
	12	20	19	13	26	19	18
	18	17	17	17	14	11	12
	24	16	16	9	23	11	18
Water excretion, ml./min.	2	1	2	1	2	2	2
	4	2	2	1	2	1	3
	6	2	3	2	3	2	2
	12	2	2	2	2	3	3
	18	2	3	2	2	2	1
	24	2	3	2	2	2	3
pH urine	2	6.2	7.7	5.9	7.2	5.4	7.1
	4	6.2	7.6	6.0	7.1	5.2	7.2
	6	5.2	7.3	5.9	6.6	5.8	6.7
	12	6.9	6.4	5.9	5.9	6.0	6.3
	18	6.9	5.5	6.3	5.7	5.8	5.2
	24	7.6	5.7	5.8	5.6	5.6	5.8

* Given as a single dose.

pensatory decrease during the period of drug response and a slight increase at the end of the 24-hour period. Quantitative differences in responses as the dose was increased were observed, but there were no significant qualitative differences in the electrolyte relationships. As a summary of our observations, the data have been tabulated in three dosage groups (Table 4), i. e., low, middle, and high. Low dose data include responses following the administration of 31, 62, 125, and 250 mg. of the drug; the middle group includes 500 and 1000 mg. doses; the high group is a 2000 mg. dose.

The greatest responses in excretion rates were observed in sodium and chloride. There was a twofold to fourfold increase at the low dose, a threefold to fivefold increase at the middle dose, and a fivefold to tenfold increase at the high dose. The magnitude of the increase in potassium excretion was about one-half (or less) that of sodium (and chloride). Ammonia excretion was depressed at all dose levels. There was an increasing rate of bicarbonate excretion as the dose was increased, varying from a twentyfold increase at the low dose level to a fortyfold increase at the high dose level. The peak excretion rate was observed at the second 2-hour period, but the total excretion rate of bicarbonate over a 24-hour period was small. Significant quantitative differences at three dose levels were not observed in titratable acidity, which averaged a fourfold increase over control. Phosphate excretion was not altered significantly.

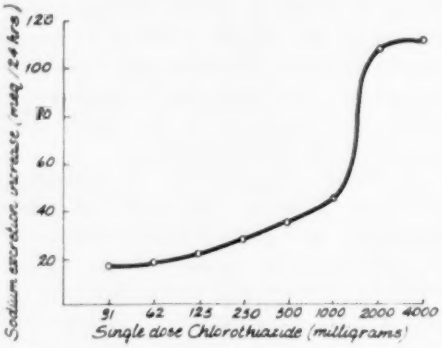


Fig. 4.—Chlorothiazide dosage response curve. There is a mild response in sodium excretion at low doses but a marked effect between 1000 and 2000 mg. dosages. The 4000 mg. dose produced no additional affect.

The small magnitude of increase in water excretion (Table 4) is a reflection of the absence of congestive failure and fluid retention in the subjects studied. The pH of the urine increased significantly immediately and began to fall four hours after the drug was administered. The increase in the excretion of total solutes did not vary significantly at the three dose levels and in general was a twofold increase (not tabulated). The experimental dose-response curve is shown in Figure 4.

II. Dosage Responses and Comparative Potency: The pilot study indicated that the effective dose lay between 1000 and 2000 mg.; hence repeated observations were made. A dose of 4000 mg. produced no toxicity but demonstrated no additional diuretic effectiveness (Fig. 4). The data are presented in Table 5.

TABLE 5.—*The Response in Sodium Excretion Following the Oral Administration of Chlorothiazide (Expressed as Milliequivalents per Twenty-Four Hours)*

Patient	1000 Mg. Dose			2000 Mg. Dose		
	Control	Drug	Increase	Control	Drug	Increase
1	42	82	40	43	167	124
2	43	89	46	41	138	97
3	46	94	48	45	162	117
4	41	90	49	48	145	97
5	48	85	37	42	174	132
6	40	86	46	45	130	85
7	45	88	43	47	147	100
8	47	91	44	46	142	96
9	45	85	40	41	143	102
10	45	93	48	47	137	90
Average	44	89	44	45	149	104
P value <			0.001			0.001

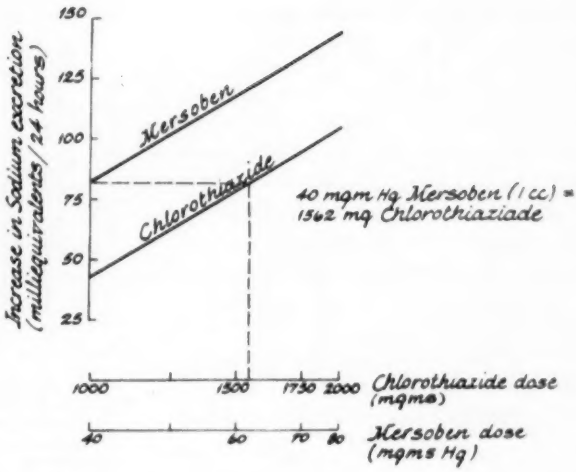


Fig. 5.—Dose-response curves for chlorothiazide versus Mersoben for determination of comparative potency. The increase in sodium excretion plotted against the dose (in logarithmic order) for a standard diuretic (Mersoben) intramuscularly administered and chlorothiazide orally administered permits a direct reading of potency (dotted line).

Since the patients were given a balanced diet containing 50 mEq. of sodium, the control excretion in the urine was approximately 90% of the dietary sodium (about 45 mEq.). The average increase in the 24-hour urinary sodium was 44 mEq. after the 1000 mg. dose and 104 mEq. after the 2000 mg. dose (Fig. 5). When these increases are compared to the increases following the administration of a standard parenteral mercurial diuretic agent (Mersoben) by the analysis of variance,[4] the dosage response curves are found to be highly significant and parallel ($P<0.001$), so that a calculation of "potency estimation" can be made.

When potency of chlorothiazide is compared with other diuretics it appears that a dose of 40 mg. of mercury equivalent of Mersoben (1 cc., I. M.) produces an increase in sodium excretion that is equivalent to 1562 mg. of chlorothiazide administered orally, or orally administered chlorothiazide at a dose of 1119 mg. is equivalent to 1 cc. of meralluride and 671 mg. of chlorothiazide is equivalent to 1 cc. of mercaptomerin (Thiomerin) administered parenterally. When both drugs are administered orally, four tablets (40 mg. mercury equivalent) of chlormerodrin are equivalent in natriuretic potency to 560 mg. of chlorothiazide.

In the patient who received 2000 mg. of chlorothiazide orally at 6 a. m. on five consecutive days, there was an increasing response in sodium excretion (as well as other electrolytes in the same pattern of relationships) over the first three days, i. e., cumulative action (Fig. 6). Although other electrolyte effects continued, there was a declining excretion of sodium on the fourth and fifth days as the body stores of this electrolyte were depleted. Since this response might be explained by the development of

TABLE 6.—*Comparative Potency of Chlorothiazide and Various Mercurial Diuretic Agents*

Drug	Route of Administration	Potency Estimation*	Dose (Mg.) of Oral Chlorothiazide Equivalent to 40 Mg. (Hg) of the Mercurial Agent (1 Cc. of Parenteral Drugs and 4 Tablets of Chlormerodrin Orally)
Mersoben	I.M.	1.3	1,562
Meralluride	I.M.	1.0	1,119
Mercaptomerin	I.M.	0.6	671
Chlormerodrin	Oral	0.5	560
Chlorothiazide	Oral	0.8	.....

* Determined from previous analysis of variance of these drugs (Ford et al.[4]).

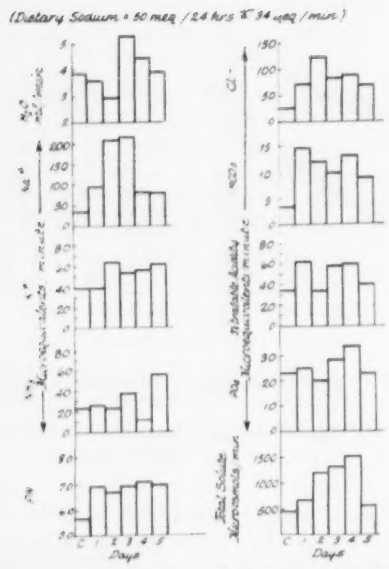


Fig. 6.—Electrolyte excretion patterns associated with the administration of chlorothiazide, 2000 mg. single dose, on five consecutive days. Repeated daily administration of chlorothiazide is accompanied by increasing sodium excretion until the body stores are depleted (when the nonedematous person is eating a diet containing 50 mEq. of sodium). Other electrolyte effects indicative of drug action persist, however.

renal tolerance to the drug, another patient (also nonedematous) was given the drug, 2000 mg. daily, for the same period. However, instead of the standard 50 mEq. sodium

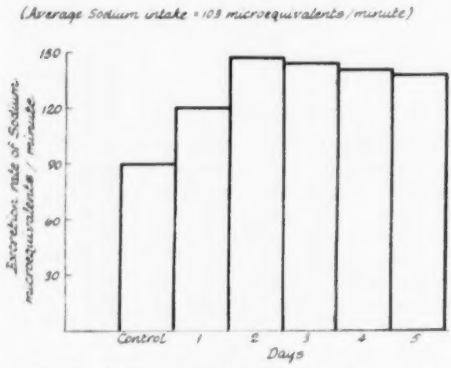


Fig. 7.—Sodium excretion following the administration of chlorothiazide, 2000 mg. single dose on five consecutive days, while nonedematous patient is eating a diet containing 150 mEq. of sodium per 24 hours. There is a continued response to the daily administration of chlorothiazide.

diet as previously used, this patient was fed a diet containing 150 mEq. of sodium. In this patient the sodium excretion remained elevated throughout the five days, although he too had a slightly declining rate of natriuresis as his body stores of sodium were lost (Fig. 7).

To further document the absence of renal tolerance to chlorothiazide, an edematous person who had been eating a low sodium (35 mEq.) diet for several years was given 500 mg. of the drug twice daily and the daily weight loss observed over a 15-day

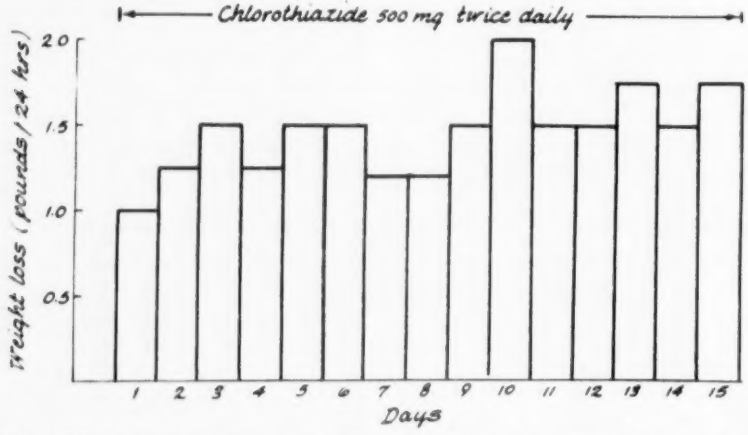


Fig. 8.—When the edematous person is given chlorothiazide daily for long periods of time, there is no loss of diuretic effectiveness as manifested by weight loss.

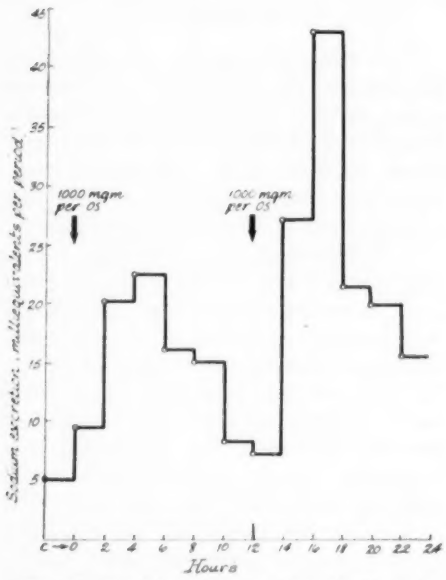


Fig. 9.—Administration of chlorothiazide twice daily (1000 mg. each dose) is associated with an augmented sodium excretion following the second dose emphasizing the clinical value of this schedule.

period (Fig. 8). The persistence of diuresis as manifest by weight loss accompanying the continuous twice daily administration of the drug is well demonstrated. This feature has further substantiating evidence in the group of chronically treated outpatients described below.

In a patient who received the drug at a dose of 1000 mg. twice within a 24-hour period the excretion pattern for sodium was repeated after the second dose in a fashion similar to that following the first dose but at a higher level (Fig. 9), and the total increase in sodium excretion per 24 hours was greater than after a single dose of 2000 mg.

To determine differences in sodium and potassium excretion when the drug is given as a single dose compared to fractional doses per 24 hours, the sodium and potassium excretion was observed in a patient who received 4000 mg. as a single dose at 6 a. m., and after a suitable recovery period (seven days) he received 1000 mg. every six hours for four doses (Fig. 10). There was a greater potassium loss on the fractional dose schedule. However, there was a greater sodium loss, indicating the advantages of fractional doses. There was no increase in the degree of natriuresis associated with the four fractional doses over the two fractional doses.

In a patient who received 2000 mg. intravenously over a 60-minute period, the pattern of sodium excretion was similar to that following the oral dose but was earlier in onset, shorter in duration, and hence less potent (Fig. 11).

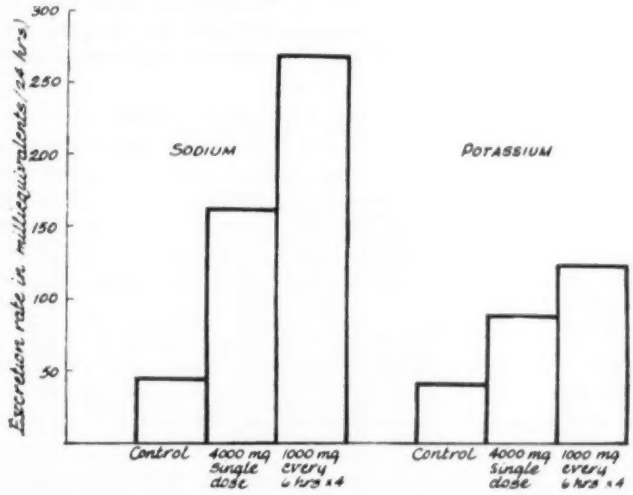


Fig. 10.—Comparative excretion patterns of sodium and potassium following single dose of chlorothiazide (4000 mg.) and fractional doses (1000 mg. q. 6 h.) for a 24-hour period. There is a greater potassium loss following chlorothiazide when administered as fractional doses, but this merely is in keeping with the greater sodium loss and proportionately is less.

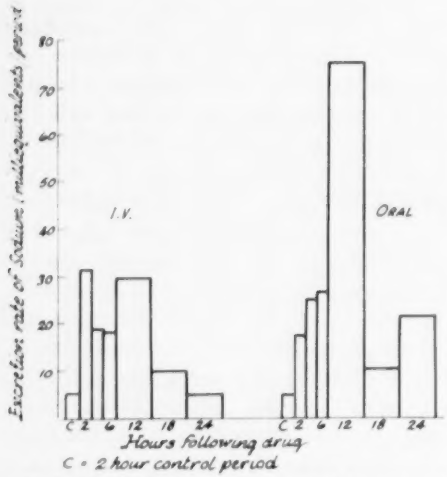


Fig. 11.—Although intravenous administration of chlorothiazide is associated with a slightly more rapid onset of increased sodium excretion, the total excretion is less than that following oral administration (2000 mg.).

C. Clinical Application.—Twenty patients with mild chronic congestive heart failure receiving chlorothiazide orally experienced adequate control comparable to that achieved with various other drugs, the commonest of which was chlormerodrin (Table 7). The dose ranged from 250 to 2000 mg. daily. No serious toxicity (nausea, diarrhea, etc.) was observed in the first three months of the daily use of the drug. Several patients complained of mild lethargy and weakness during the period of maximum diuresis.

Comment

Chlorothiazide represents an advance in the search for clinically effective oral diuretic agents that are nonmercurial and non-carbonic-anhydrase-inhibitors.[5] The agent is a potent inhibitor of the renal tubular reabsorption of sodium after oral administration (Tables 2 and 3). It causes a minimal excretion of bicarbonate and, therefore, a considerable excretion of chloride (Figs. 2 and 3). The excretion of potassium is influenced to a smaller degree than it is by carbonic anhydrase inhibitors, a distinct advantage. An oral dose has a rapid onset of action within 2 hours and a duration of action of less than 12 hours (Figs. 2 and 3). It is recurrently effective when administered in repeated daily doses (Figs. 6, 7, and 8). It does not produce metabolic acidosis or other physiological or pharmacodynamic side-effects, so that it has a high therapeutic index (and a low toxicity). Comparison of the enhanced sodium excretion following intravenous and oral administration indicates that the latter is the more effective method for clinical use (Fig. 11). This is compatible with data[5] showing that the drug is almost totally excreted within 6 hours following intravenous administration, whereas with the oral dose one-half is excreted in 24 hours and excretion is completed in 48 hours.

Because of the structural formula (Fig. 1) of chlorothiazide and the electrolyte excretion patterns following its administration

TABLE 7.—*Clinical Comparison of Chlorothiazide in the Treatment of Twenty Ambulatory Patients with Chronic Congestive Heart Failure*

Patient	Chlorothiazide, Mg.	Previous Therapy Replaced	Side-Reactions
1	250 q.d.	Chlormerodrin, 2 tablets daily	None
2	250 q.d.	Chlormerodrin, 2 tablets daily	None
3	250 q.d.	Chlormerodrin, 2 tablets daily	None
4	250 q.d.	Chlormerodrin, 2 tablets daily	None
5	250 q.d.	Chlormerodrin, 2 tablest daily	None
6	250 b.i.d.	Chlormerodrin, 4 tablets daily	None
7	250 b.i.d.	Chlormerodrin, 4 tablets daily	None
8	250 b.i.d.	Chlormerodrin, 4 tablets daily	None
9	250 b.i.d.	Chlormerodrin, 4 tablets daily	None
10	250 b.i.d.	Chlormerodrin, 4 tablets daily	None
11	500 b.i.d.	Chlormerodrin, 4 tablets daily	None
12	500 b.i.d.	Mercaptomerin, 1 cc. Hg 3 days	None
13	500 b.i.d.	Chlormerodrin, 4 tablets daily	None
14	500 b.i.d.	Chlormerodrin, 4 tablets daily	None
15	500 b.i.d.	Chlormerodrin, 4 tablets daily	None
16	1000 b.i.d.	Chlormerodrin, 4 tablets daily	None
17	1000 b.i.d.	Meralluride, 2 cc. I.M. weekly	None
18	1000 b.i.d.	Chlormerodrin, 4 tablets daily	None
19	1000 b.i.d.	Chlormerodrin, 8 tablets daily	None
20	1000 b.i.d.	Chlormerodrin, 8 tablets daily	None

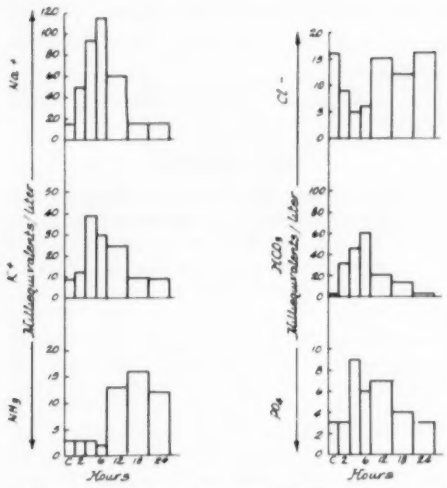


Fig. 12.—Patterns of excretion following concurrent administration of meralluride (1 cc. intramuscularly) plus acetazolamide (250 mg. orally). There is a suppression of the loss of chloride due to a mercurial agent when a carbonic anhydrase inhibitor is administered concurrently. The loss of bicarbonate is greater with this combination than with chlorothiazide. This pattern of electrolyte excretion is significantly different from that observed following chlorothiazide.

to patients, one might postulate that it represented a combination of mercurial and carbonic anhydrase inhibitor diuretic effects. Maren demonstrated that the chloride loss due to mercurial diuretics was suppressed by the concurrent administration of a carbonic anhydrase inhibitor, acetazolamide.[6] We have in essence repeated his experiment and observed the electrolyte excretion patterns in a fashion similar to those of the current study (Fig. 12). Our data are in accord with those of Maren in showing a maximum chloride effect which is only one-half of sodium. The bicarbonate loss was four to six times greater with this combination than with chlorothiazide. Thus the electrolyte excretion patterns imply basically different modes of action of these diuretic agents.

Certain clinical implications may be derived from the data of this study. The dosage-response curve relating increasing amounts of chlorothiazide to sodium excretion indicates that the effective clinical dose (Fig. 4) is between 1000 and 2000 mg. (as a single dose). A single dose of 4000 mg. did not produce a significantly greater effect than the 2000 mg. dose. This determination permits a comparison between various other mercurial diuretics. Thus, 1119 mg. of orally administered chlorothiazide produces an increased sodium excretion comparable to 1 ml. of meralluride administered intramuscularly. Four tablets, equivalent to 40 mg. of Hg of chlormerodrin, orally administered is comparable to 560 mg. of chlorothiazide administered by the same route. This dose is roughly twice as potent as acetazolamide (Diamox) at its maximal effective dose. Administration of chlorothiazide at 12-hour intervals results in a greater increase in sodium excretion than the same total dose administered as a single dose per 24 hours (Fig. 9). However, there is no significant advantage in a 6-hour dose schedule over the 12-hour schedule (Fig. 10). The potassium loss does not increase proportionately to the sodium loss in the latter. Further, repeated daily administration of the drug is accompanied by continuous effectiveness (in contrast to carbonic anhydrase inhibitors). Clinical experience over a three-month period indicates that the drug is effective in replacing currently available orally and parenterally administered diuretic agents in the management of chronic congestive heart failure.

The data of this study indicate that chlorothiazide at a daily divided (twice) dose of 1000 mg. (range, 500-2000 mg.) is effective as an oral diuretic agent with no demonstrable toxicity.

Summary and Conclusions

Chlorothiazide (6-chloro-7-sulfamyl-1,2,4-benzothiadiozine-1,1-dioxide) is an orally effective diuretic agent with a major action on sodium excretion similar to the mercurials but with additional and differing electrolyte excretion effects.

Electrolyte excretion studies indicate that the predominant influence is on the renal excretion of sodium and chloride, with a smaller effect on the excretion of potassium

and bicarbonate in the presence of an alkaline urine.

Upon oral administration, the onset of action is within 2 hours and the duration of action is approximately 6 to 12 hours. It is repeatedly effective on continuous daily or twice daily administration. Oral doses are more effective for increasing the total 24-hour excretion of sodium than are rapidly excreted intravenous doses.

Comparative potency of chlorothiazide and other currently available diuretic agents is presented. A dose of approximately 500 mg. of chlorothiazide is roughly equivalent to four tablets (40 mg.) of chlormerodrin (Neohydrin) in ability to augment sodium excretion and is roughly twice as potent as acetazolamide (Diamox). A dose of slightly more than 1000 mg. of chlorothiazide (oral) is equivalent to 1 cc. of meralluride (Mercuhydrin) administered intramuscularly.

Clinical experience indicates that an average dose which is effective in controlling chronic congestive heart failure is 500 mg. given twice daily. The diuretic response increases progressively as the dose is increased to 2000 mg. (or more). No toxicity has been observed after three months of continuous drug administration. Maximum doses (in excess of 2000 mg.) have not demonstrated increased effectiveness. (Doses of 4000 mg. did not produce any evidence of toxicity.)

Baylor University College of Medicine, Texas Medical Center (Dr. Moyer).

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Gross Hematuria in Sickle-Cell Trait

A Report of Eight Cases

COL. RICHARD I. CRONE (MC); CAPT. SAMUEL C. JEFFERSON (MC); 1ST LIEUT. VINCENT J. PILEGGI (MC), and COL. EARL C. LOWRY (MC), U. S. Army

The clinical manifestations of sickle-cell anemia have been known for many years. It was first suggested by Bauer and Fisher,[1] in 1943, when they described manifestations noted in the "nonanemic variety of sickle-cell disease," that sickle-cell trait, the heterozygous state of the sickle-cell gene, can cause symptoms. Since that time an increasing number of reports have stressed the point that vascular occlusions leading to clinical symptoms may occur in persons harboring sickle-cell trait or in others demonstrating newly discovered abnormal hemoglobin variants.

Only recently have sickle-cell disease and its genetic variants been demonstrated as a cause of gross hematuria. Only too often hematuria without readily demonstrable cause is a major concern to the urologist. Frequently these cases are first seen by the internist or general practitioner, who refers them for urologic investigation only to have complete genitourinary clearance given. Whenever so-called essential, or idiopathic, hematuria is diagnosed in a Negro patient, one must always suspect sickle-cell hemoglobin abnormalities as a possible etiological cause.

Abel and Brown,[2] in 1948, were the first to report gross hematuria in a patient with sickle-cell anemia, and, in 1950, Goodwin, Alston, and Semans[3] suggested sickle-cell disease as one of the underlying causes of so-called essential hematuria in a Negro and reported seven cases associated with the positive sickling phenomenon. In 1952, Harrison and Harrison[4] presented a series of nine cases of hematuria associated with sickle-cell abnormalities. Lund, Cordonnier, and Forbes,[5] in 1954, reported seven cases believed to be associated with sickle-cell traits based on laboratory differentiation by the technique described by Singer, Chernoff, and Singer.[6] This method utilizes an alkali denaturation process which destroys normal hemoglobin in one minute but does not destroy fetal hemoglobin. Characteristically, fetal hemoglobin is present in normal amounts (up to 2%)[7] when the abnormal hemoglobin exists in the heterozygous or trait pattern. In sickle-cell anemia (S-S) and such combination patterns as S-C and S-thalassemia fetal hemoglobin is usually present in increased amounts.

In reviewing the literature it becomes evident that it is difficult, and at times impossible, to ascertain whether or not the reported cases of hematuria associated with the sickle-cell phenomenon are actually manifestations of sickle-cell anemia, the trait only, or sickle-cell hemoglobin in combination with other abnormal hemoglobins. It would appear that only by proper electrophoretic study and hemoglobin solubility tests can the definite hemoglobin pattern be established. Several reported series have appeared in the literature where the hemoglobin patterns have been established. Ranney,[8] in 1953, reported two cases of hematuria associated with sickle-cell hemoglobin C disease. Smith and Conley,[9] in the same year, added two more cases with the S-C pattern. In 1954, in another study,[10] they reported results of their reexamination of four of Goodwin's[3] seven

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Department of Medicine and the Pathology and Urology Services, Letterman Army Hospital, San Francisco.

cases and found two with sickle-cell trait, one with sickle-cell anemia, and one with sickle-cell hemoglobin C disease. In this survey they also identified one case of sickle-cell thalassemia with hematuria and subarachnoid hemorrhage. The same year, Goldman et al.[11] reported hematuria in six patients with sickle-cell traits and in three with sickle-cell hemoglobin C disease. Chapman et al.,[12] in 1955, reported five more S-A patterns and three with S-C patterns. Chernoff,[13] in the same year, stated that he had seen 7 cases of sickle-cell trait with hematuria in his own clinic over the previous two years and knew of 25 others in whom this complication had developed.

From these reports and observations it becomes apparent that cases of hematuria associated with sickle-cell trait (S-A) are not a rare occurrence and that increasing numbers of such cases will be added to the literature as the determination of hemoglobin patterns becomes a more universally adopted procedure. We should like to report eight cases, seven of which have been diagnosed and studied at our hospital in the last three years and one from the private practice of Dr. Ralph Wallerstein.* All of these cases have been established as sickle-cell traits by paper electrophoresis with the Spinco Model R apparatus. Results are listed in the Table.

Report of Cases

Case 1.—A 26-year-old Negro male soldier was admitted to the hospital on March 9, 1954, because of recurrent hematuria. He was well until 1951, when he had the onset of severe sharp periumbilical pain associated with gaseous distention. He was hospitalized for three days, during which time his symptoms abated, and he was returned to duty. Shortly thereafter he had recurrence of his abdominal distress, associated with intermittent gross hematuria. He was again hospitalized in 1953 and was found to have a positive sickle-cell preparation. Cystoscopy and excretory and retrograde pyelograms were normal. He was returned to duty but continued to have intermittent episodes of gross hematuria, and he was readmitted for further evaluation.

Physical examination revealed a thin but well-developed Negro man in no apparent distress. The liver, spleen, and kidneys were not palpable, and there was no abdominal tenderness. The remainder of the physical examination was within normal limits. Laboratory data revealed a red blood cell count of 4,970,000 per cubic millimeter and a hemoglobin value of 14.7 gm. per 100 cc. The white blood cell count was 4850 per cubic millimeter with 54% neutrophils, 43% lymphocytes, 1% monocytes, and 2% eosinophils. The platelet count was 224,000 per cubic millimeter; the bleeding and clotting times and the osmotic fragility test were normal. The urine was loaded with red blood cells, many of which revealed sickle forms. Repeated sickle-cell preparations revealed 85% to 95% sickling. Hemoglobin electrophoresis demonstrated an S-A pattern. Several 24-hour urine cultures for tubercle bacilli were negative.

During his hospitalization he continued to have intermittent gross hematuria. Since his urological examination one year prior had been completely normal, it was not repeated. His hematuria was considered to be due to the presence of sickle-cell trait, and he was returned to duty with a recommendation for further follow-up.

Case 2.—A 22-year-old Negro woman was first admitted to the hospital on Dec. 27, 1954 because of painless gross hematuria. She had been well until several days prior to her admission, when she developed gross hematuria, asymptomatic except for mild nausea. Past history and family history were noncontributory.

Physical examination was completely within normal limits. Laboratory data revealed a white blood cell count of 10,700 per cubic millimeter, with 71% neutrophils, 28% lymphocytes, and 1% eosinophils. The hemoglobin was 11.3 gm. per 100 cc., and the hematocrit, 34%. Urinalysis revealed 3+ albumin and many red blood cells per high-power field. Cystoscopy demonstrated several bleeding ulcerative lesions in the bladder, but there was no blood coming from either ureteral orifice. Retrograde pyelograms revealed slightly enlarged kidneys, with some tortuosity and dilatation of both ureters. Several 24-hour urine cultures for tubercle bacilli were negative.

*Assistant Clinical Professor of Medicine, University of California School of Medicine.

Results of Paper Electrophoresis in Eight Cases

Case	Hgb. A, %	Hgb. S, %
1	61	39
2	63	37
3	Present but not quantitated	Present but not quantitated
4	55	45
5	77	23
6	57	43
7	63	37
8	Present but not quantitated	Present but not quantitated

She was given penicillin, with some resulting diminution of the hematuria, and was discharged to continue antibiotic therapy at home. The hematuria, however, became increasingly severer, and she was readmitted three weeks later. Cystoscopy was performed again and was normal except for blood coming from the right ureteral orifice. Retrograde pyelograms were within normal limits. Hemoglobin was 9.2 gm. per 100 cc. Stained blood smear revealed adequate platelets. A sickle-cell preparation was positive, and hemoglobin electrophoresis obtained at a later date demonstrated S-A pattern. Urine culture revealed Klebsiella organisms. She was given nitrofurantoin (Furadantin) therapy. During her hospitalization she continued to have hematuria, though it diminished in intensity; consequently, she was discharged to be followed at regular intervals in the urology clinic. In March, 1955, she was readmitted for further evaluation; cystoscopy and retrograde pyelograms were normal except for blood coming from the right ureteral orifice. It was felt that her hematuria was due to the presence of sickle-cell trait, and no therapy was instituted. Since that time the patient has continued to have intermittent gross hematuria and a moderate anemia, with hemoglobins ranging from 10 to 12 gm. per 100 cc.

CASE 3.—A 19-year-old Negro male soldier was admitted to the hospital on April 25, 1955, because of hematuria. He was in good health until four years previously, when he had a brief episode of painless gross hematuria which subsided spontaneously. He was subsequently well until several days prior to his admission, when he began to pass "wine-colored" urine and was admitted for evaluation.

Physical examination was within normal limits except for a blood pressure of 150/100. Laboratory data revealed a white blood cell count of 7800 per cubic millimeter. Differential count was not done. The hemoglobin was 13.6 gm. per 100 cc., and the hematocrit, 40%. Cystoscopy was normal except for blood coming from the right ureteral orifice, and retrograde pyelograms were normal. A 24-hour urine culture for tubercle bacilli was negative. Several sickle-cell preparations revealed 90% to 98% sickling, and hemoglobin electrophoresis demonstrated S-A pattern. Blood smears revealed adequate platelets.

During his hospitalization he remained asymptomatic, though he continued to have gross hematuria. It was felt that his hematuria was due to the presence of sickle-cell trait, and as it did not abate he was given a medical discharge from the service.

CASE 4.—A 24-year-old Negro male soldier was admitted to the hospital on April 14, 1955, because of malaise, fever, cough, and nasal discharge of one day's duration. Three days later he had the onset of gross hematuria associated with generalized cramping abdominal pain and sharp throbbing right flank pain. Because of these symptoms he was transferred to this hospital for further evaluation.

Physical examination revealed a well-developed well-nourished Negro man. There was slight tenderness in both upper quadrants of the abdomen; no abnormal masses were present. Laboratory data revealed a white blood cell count of 6600 per cubic millimeter. Differential count was not obtained. The hemoglobin was 12.9 gm. per 100 cc., and the hematocrit, 38%. Subsequent blood smears revealed adequate platelets. Initial urinalysis revealed 4+ albumin and many red blood cells per high-power field. A sickle-cell preparation revealed 85% sickling, and hemoglobin electrophoresis demonstrated S-A pattern.

After the first few days the patient became asymptomatic and his urine cleared completely. Cystoscopy and retrograde pyelography were normal. It was felt that the hematuria was due to the presence of sickle-cell trait, and he was returned to duty.

CASE 5.—A 19-year-old Negro male soldier was initially admitted to a station hospital on Aug. 2, 1955, because of painless hematuria. Four months prior to that time he had had a similar episode, which subsided spontaneously after one day. He was found to have 2+ albuminuria and gross hematuria. Urine culture revealed paracolon bacilli, and he was given sulfisoxazole (Gantrisin). His urine cleared subsequently, only to have the gross hematuria recur. He was therefore transferred to this hospital for further evaluation. Past history revealed that he had had pericarditis in 1954 and two episodes of gonorrhea without complications.

Physical examination was within normal limits. Laboratory data revealed a white blood cell count of 5600 per cubic millimeter; differential count was not obtained. The hemoglobin was 14.9 gm. per 100 cc., and the hematocrit, 44%. Blood smears revealed adequate platelets. Repeated urinalyses revealed 1+ to 2+ albumin and many red blood cells per highpower field. Initial urine culture revealed Escherichia coli and Proteus bacilli; a 24-hour urine culture for tubercle bacilli was negative. Repeated sickle-cell tests revealed almost 100% sickling, and hemoglobin electrophoresis demonstrated S-A pattern. Cystoscopy revealed blood coming from both ureteral orifices, and retrograde pyelograms were normal.

The patient continued to have gross hematuria during his entire hospital course. Because of the positive urine cultures he was given nitrofurantoin, and subsequent cultures were negative. It was believed that the hematuria, which persisted, was due to the presence of sickle-cell trait, and the patient was given a medical discharge from the service.

CASE 6.—A 22-year-old Negro woman was admitted to the hospital on Sept. 2, 1955, because of gross hematuria of one day's duration associated with chills, fever, and bilateral backache. The patient stated that in November, 1954, she had received antibiotics for a similar episode during the eighth month of pregnancy. Past history and family history were noncontributory.

Physical examination revealed a well-developed well-nourished, Negro woman. Oral temperature was 100.2 F. There was slight bilateral costovertebral angle tenderness, most pronounced on the left. Laboratory data revealed a white blood cell count of 12,250 per cubic millimeter, with 81% neutrophils, 9% lymphocytes, 9% monocytes, and 1% basophils. The hemoglobin was 12.0 gm. per 100 cc., and the hematocrit, 45%. Blood smears revealed adequate platelets. Urinalysis revealed 2+ albumin and innumerable red blood cells per high-power field. Urine culture revealed Aerobacter aerogenes. Sickle cell preparations revealed 80% to 100% sickling, and hemoglobin electrophoresis demonstrated S-A pattern. Cystoscopy and retrograde and excretory pyelograms were normal.

After urine cultures were done the patient was given chlortetracycline (Aureomycin), with subsidence of her symptoms and clearing of the urine within 24 to 48 hours. It was felt that the hematuria was most likely due to the sickle-cell trait, precipitated perhaps by the urinary tract infection. She was discharged from the hospital, and follow-up revealed that she had remained completely asymptomatic.

CASE 7.—A 39-year-old Negro soldier was admitted to the hospital on June 12, 1955, because of hematuria of undetermined etiology. Eight days prior to hospitalization he was involved in an automobile accident but denied any injury. Two days later, however, he noted the onset of painless gross hematuria and was admitted to an army station hospital. Investigation was negative except for the hematuria and a positive serologic test. His hematuria gradually subsided, and he was transferred to this hospital for further investigation. Family history and past history were noncontributory.

Physical examination revealed a well-nourished Negro man in no distress. The liver, spleen, and kidneys were not palpable, and there was no abdominal or costovertebral tenderness. Laboratory data revealed a white blood cell count of 6700 per cubic millimeter and a hemoglobin value of 14.7 gm. per 100 cc. Urinalysis on admission was normal. The blood serologic test was positive. A sickle-cell preparation revealed almost 100% sickling on one occasion and was negative on another. Blood smears revealed adequate platelets. Hemoglobin electrophoresis revealed S-A pattern. Intravenous pyelograms were normal. A 24-hour urine culture for tubercle bacilli was negative. An excretory pyelogram was normal. Cystoscopy and retrograde pyelograms were not done at this time.

Shortly after admission to the hospital the patient began to have gross hematuria again, which subsided spontaneously in a few days. Sickled red blood cells were seen in the urine. Investigation was negative except for the presence of the sickle-cell trait. Further history revealed that the patient had had known positive blood serologic tests for several years, with adequate treatment and negative spinal fluid examinations. He was returned to duty June 28, with recommendations for periodic outpatient checkups and instructions to return to the hospital if the hematuria recurred.

CASE 8 (Provided by Dr. Ralph O. Wallerstein).—A 30-year-old Negro man had the spontaneous onset of gross hematuria 10 years ago. Since that time he has had almost continual gross hematuria, occasionally associated with dysuria. At times the patient passed small clots of blood and had three to four episodes of aching left flank pain per year, which would persist for one to two weeks. Past history and family history were noncontributory.

Physical examination was entirely within normal limits. Laboratory data revealed a white blood cell count of 8500 per cubic millimeter, with 66% neutrophils, 26% lymphocytes, 2% monocytes, and 6% eosinophils. The red blood cell count was 4,600,000 per cubic millimeter, with a hemoglobin value of 14.3 gm. per 100 cc. The platelet count was 200,000, and reticulocytes, 0.6%. Urinalysis showed a trace of albumin, and the urine was loaded with red blood cells. A sickle-cell preparation was positive, and hemoglobin electrophoresis revealed an S-A hemoglobin pattern. Frequent and extensive urologic work-ups, including cystoscopy and intravenous and retrograde pyelograms, had been normal except for persistent hematuria from the left ureteral orifice.

Comment

It is apparent that Cases 2, 5, and 6 had associated urinary tract infections which may have been an aggravating factor in precipitating the bleeding. In Case 6 the bleeding ceased after the infection was eliminated, while in the other two the gross hematuria continued after all demonstrable infection was cleared. The possibility that gross hematuria in the sickle-cell diseases may not always be due to the underlying hemoglobin abnormality is of course always to be considered. We should like to emphasize that a careful urologic examination is always mandatory. It should include de-

tailed cystoscopy, urograms, differential urine examinations, and cultures when indicated. Other systemic diseases, including possible coagulation defects, should also be ruled out. When the episodes of bleeding recur, repeat urologic examination at appropriate intervals should be considered in order to eliminate tumor, recurring infection, or some vascular anomaly.

A positive sickle-cell test was exhibited in all our cases on the first attempt. It is most important to realize that just one sickle-cell preparation is not an entirely reliable screening test when sickle-cell disease is suspected. In sickle-cell trait, sealed preparations may take 24 hours or longer before the characteristic changes are manifest. The amount of sickling varies at different intervals and may be negative at times, as demonstrated in Case 7. The sickling phenomenon is best demonstrated in preparations employing the use of fresh 2% aqueous sodium bisulfite or some other reducing agent. Occasionally sickled red blood cells will be seen in the urine. The diagnosis in some of the reported cases in the literature has been suggested by observation of sickled cells in tissue sections from the removed kidneys.[2-5,12,14] In tissues fixed in formalin or Zenker's solution the sickle cells will "freeze" at any morphological stage and the red blood cells will not sickle directly.[15] It should be recalled that in any examination for sickling exposure of unfixed preparations to air can revert sickled forms to normal-appearing discoid shapes. The finding of target cells in the stained blood smear should alert the wary clinician to the possibility of a combination of the sickle-cell gene with the hemoglobin C or thalassemia gene. Only by electrophoretic determination and hemoglobin solubility tests can the exact nature of the hemoglobin abnormality be ascertained with laboratory certainty.

In none of our cases were there filling defects in the calyceal systems or pelves. The occurrence of such defects has lead to the erroneous diagnosis of kidney tumor and subsequent nephrectomy.

Accounts of demonstrable pathology in the kidneys are of interest. Diggs and Ching,[16] in 1934, reported congestion, thrombosis, hemosiderosis, infarction necrosis, and scars in the parenchyma from healed lesions. Kimmelstiel[17] has emphasized that ischemic infarction of organs in sickle-cell disease is often unaccompanied by vascular thromboses. He theorizes that the primary mechanism is peripheral vascular spasm which may lead directly to the ischemic necrosis or may be followed by secondary capillary dilatation or stasis. These secondary changes then lead to anoxia, which produces further sickling, organic change to the vessel walls, thrombosis, and finally superimposed infarctions. Pratt-Thomas and Switzer[18] likewise believe that thrombi are the exception rather than the rule and that, since the result of tissue ischemia may be found without definite mechanical obstruction, this would support the theory that the abnormally shaped sickle cells can form agglutinated clumps, producing actual obstruction and infarction without thromboses. This is well substantiated by many, and the main difference in opinion appears to be whether the sickling is a primary or secondary process. Once initiated, however, it is a potent factor in leading to tissue ischemia. To attribute the bleeding entirely to the bizarre and somewhat more rigid sickled erythrocytes seems untenable, and it would appear that there must be other factors not yet understood which must be involved. As is evident from perusal of the literature, bleeding is usually unilateral, particularly on the left side. The possibility of congenital anomalies which often occur in these disorders might be a factor. Chernoff[13] states that some investigators postulate an anatomic or structural predisposition of the left kidney. A vascular defect could be an aggravating factor in an organ such as the kidney, characterized by tissue with thin-walled vessels in areas of low oxygen tension.

With the exact mechanism of the bleeding being poorly understood, treatment is difficult to outline on any sound basis. Harrison

and Harrison[4] carried out nephrectomy in four cases without complications. They concluded from their experience and from consideration of the modern advances in anesthetic and surgical techniques that nephrectomy was the treatment of choice in patients with sickle-cell disease who suffer from massive unilateral bleeding. Bauer,[19] however, in 1940, stressed the fact that these patients were poor surgical risks and particularly so when the disease was unrecognized. When we realize that the kidney is particularly susceptible to the effects of shock and ischemia and that anoxia is a potent factor in precipitating the sickling phenomenon, the possible dangers inherent in anesthesia and surgery must be considered. A potent argument certainly comes to mind when one is faced with this problem of the possibility of bleeding at a later date from the remaining kidney. Lund et al.[5] cite one of their cases in which there was recurrence of hematuria in the remaining kidney four years after the other kidney had been removed for the same complaint. It would appear that nephrectomy should be advised only in those cases where one is dealing with protracted and repeated bleeding and progressive severe anemia which is inadequately controlled by repeated blood transfusions and where all other possible methods to control the bleeding have failed. Greenberg and Kass[20] have recently made the observation that the intravenous administration of large amounts of sodium bicarbonate (1.5 to 3.5 mEq. per kilogram per hour) to four patients during painful crises resulted in a transient decrease in the susceptibility to sickling in vitro and relieved the pain in three of the cases within one hour. We believe this procedure should be tried in cases of protracted hematuria associated with the sickle-cell phenomenon.

Summary and Conclusions

Eight cases of gross hematuria associated with electrophoretically proven sickle-cell trait are presented.

In view of negative findings implicating any other etiological cause, the hematuria is most likely due to pathological changes secondary to the hemoglobin abnormality.

A brief review of the literature would indicate that gross hematuria associated with the sickle-cell trait (S-A) and other sickle-cell abnormal hemoglobin combinations, particularly S-C, is undoubtedly commoner than generally realized.

The pathological mechanisms involved in the causation of the renal bleeding are not completely understood.

Treatment in general would appear to be mainly supportive, with nephrectomy reserved as a live-saving measure when all other measures have failed to stop the bleeding.

2d General Hospital, APO 180, New York (Colonel Crone).

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Streptococcal Disease and Rheumatic Fever in Air Force Recruits

I. Epidemiology and Clinical Picture of Acute Rheumatic Fever

CAPT. HAROLD P. LAZAR (MC); CAPT. GERALD I. MAAS (MC), U.S.A.F.; WENDELL R. LIPSCOMB, M.D., Berkeley, Calif.; COL. JAMES H. HAMMOND (MC), U.S.A.F., Parks Air Force Base, Calif., and LOWELL A. RANTZ, M.D., San Francisco

Recent investigations into the etiology and pathogenesis of acute rheumatic fever [1] have solidified the concept of a close relationship with streptococcal disease previously emphasized by numerous studies,[2-8] many involving military populations.

A unique opportunity to study streptococcal disease and acute rheumatic fever in epidemic proportions presented itself at a large northern California Air Force basic training center in the first half of 1955, when 58 cases of acute rheumatic fever were observed.

Epidemiologic investigations were pursued and detailed observations made of the clinical and laboratory features of acute rheumatic fever in epidemic form. Clinical impressions were also derived relating to the efficacy of salicylate and steroid therapy in young adult males, although a rigorously controlled study was not undertaken.

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From the Department of Medicine and the Streptococcal Disease Control Board, 3275th U. S. A. F. Hospital, Parks Air Force Base, Calif., and the Department of Medicine, Stanford University School of Medicine, San Francisco. Aided by Grant No. H 700 from the National Heart Institute, National Institutes of Health.

Streptococcal Disease Control Coordinator; now at Michael Reese Hospital, Chicago; present address, 3550 Pine Grove Ave., Chicago 13 (Capt. Lazar). Member, Streptococcal Disease Control Board (Capt. Maas). Formerly, Preventive Medicine Officer, Parks Air Force Base, Calif.; present address, California State Department of Health, 2151 Berkeley Way, Berkeley 4, Calif. (Dr. Lipscomb). Chief, Department of Medicine, and Streptococcal Disease Control Officer (Col. Hammond). Professor of Medicine, Stanford University School of Medicine, and Consultant, 3275th U. S. A. F. Hospital, Parks Air Force Base, Calif. (Dr. Rantz).

Background

Parks Air Force Base is a large U. S. A. F. installation located in the Amador Valley in a normally warm agricultural area about 15 miles east of Oakland, Calif. Formerly Camp Shoemaker, a Seabee Training Center in World War II when utilized by the U. S. Navy, it was until September, 1956, one of several basic training centers being operated by the U. S. Air Force, serving the Far West and receiving recruits from as far east as Illinois. As an additional function, Parks has the important role of Far East overseas processing center for the Air Force.

While there are no good statistics to document the true incidence of acute rheumatic fever, it has been estimated that only one in four California physicians will see a case of rheumatic fever each year.[9] A total of 29 new cases were reported in nearby San Francisco in all of 1955.[10] It was quite remarkable, therefore, when 58 well-documented cases of acute rheumatic fever were accumulated in a six-month period, beginning Jan. 1, 1955. Utilizing the oft-quoted figure that 3% of untreated or inadequately treated streptococcal infections will eventuate in acute rheumatic fever, it becomes immediately apparent that, in view of obviously inadequate preparation for recognizing and reporting streptococcal infections which might herald a rheumatic fever outbreak, there must have occurred approxi-

TABLE 1.—*Rheumatic Fever Morbidity, U. S. Air Force*

		Incidence/1,000/Annum
Parks Air Force Base	1953	1.8
	1954	0.5
(Jan.-June)	1955	4.1
U. S. Air Force 1951 (Jan.-June)		
Continental United States		1.4
Worldwide		1.1

mately 2000 untreated streptococcal infections! That these 58 cases represent a formidable epidemic is apparent from a consideration of statistical comparisons (Table 1).

Epidemiologic Studies

An unusual coincidental set of circumstances contributed to the development of the respiratory disease problem. Effective Jan. 31, 1955, the Federal Government discontinued GI Bill of Rights benefits to entering servicemen. Advance publicity of this fact led to a late January upsurge in enlistments, so that the recruit strength reached a peak level of approximately 8000 in mid-February. Allowing one to two weeks for contact with the virulent Streptococcus plus the two- or three-week latent period, the period of peak incidence is established in mid-March. This can be seen by reference to Figure 1. One of us (H. P. L.) had the unique experience of serving as Medical Officer of the Day and admitting five patients with acute rheumatic fever in a 24-hour period in March, 1955.

Convincing evidence of the ease and rapidity of acquisition of the streptococcal carrier state was obtained by one of us (W. R. L.), who interviewed and cultured at random three flights of approximately 55 men each, with varying lengths of residence on the base. As can be observed in Figure 2, there was a striking increase in the percentage of recruit dispensary visits and complaints of sore throats, so that 50% of a flight with 60 days' residence had complained of a sore throat. Even more striking is the objective evidence of increasing con-

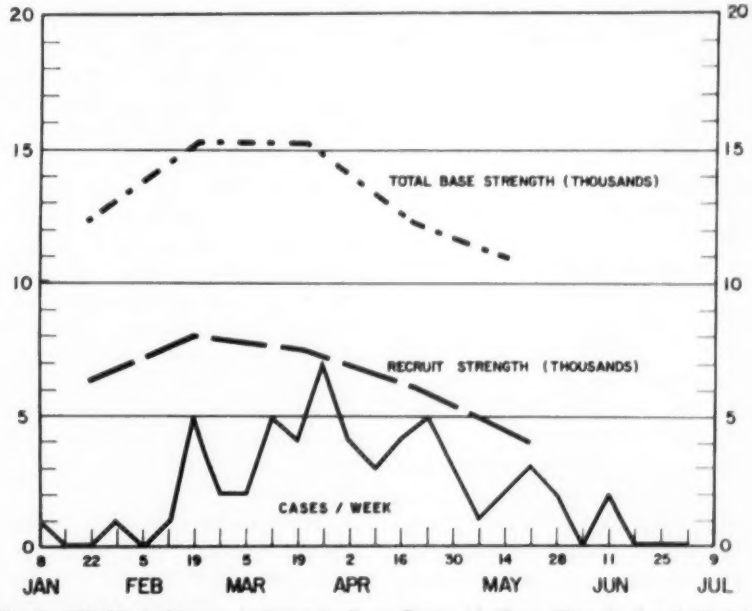


Fig. 1.—Weekly incidence of rheumatic fever, Parks Air Force Base, in first half of 1955.

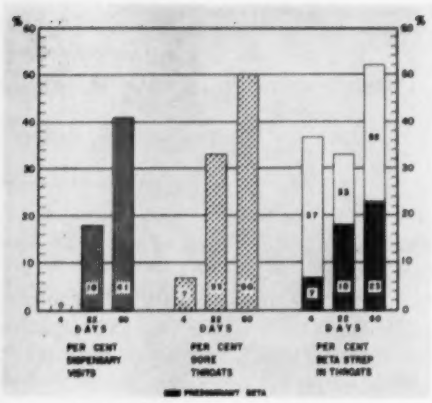


Fig. 2.—Acquisition of streptococcal carrier state by three flights with varying lengths of residence at Parks Air Force Base, ascertained by interview and throat culture, 1955.

version to the streptococcal carrier state in proportion to length of residence at Parks. Approximately one-third of the 4-day and 22-day flights harbored Group A streptococci in their throats, while about one-half of the 60-day flight were carriers. A more semiquantitative measure of the carrier state, the presence of a predominantly β-streptococcic flora, revealed percentages rising from 7% in the 4-day flight to 23% in the 60-day flight. A generous sampling of 49 hospital corpsmen, in May, 1955, revealed that 12.2% were streptococcal carriers.

After consideration of the aforementioned studies and an evaluation of the severity of rheumatic fever attack rate it was decided that the entire basic training population be given 250,000 units of oral buffered crystalline penicillin G twice daily for 10 days—a scheme previously evaluated by both the Air Force and the Navy.[4,5] This was accomplished by late May, by which time the rheumatic fever epidemic had largely run its course.

Subsequent carrier studies were made in the Fall of 1955 in the search for a reservoir group. Two groups intimately associated with the basic trainees are the training instructors and the mess hall personnel. Generous sampling of both groups by nose and throat culture revealed insignificant numbers of carriers. Since the recruits do not leave the base during the period of streptococcal disease exposure, one can only assume that the organism is imported with new recruits or lies dormant on the base in some unrecognized fashion.

Clinical and Laboratory Findings in Epidemic Acute Rheumatic Fever

With one exception, all patients were basic trainees and fell into the 17- to 21-year-old range. As a guide in diagnosis, the new modified criteria of T. Duckett Jones [11] were followed. The major criteria were (1) carditis, (2) polyarthritis, (3) chorea, (4) subcutaneous nodules, (5) erythema marginatum. The minor criteria were (1) fever; (2) arthralgia; (3) prolonged P-R interval in the electrocardiogram; (4) increased erythrocyte sedimentation rate, presence of C-reactive protein, or leukocytosis; (5) evidence of preceding β-hemolytic streptococcal infection; (6) previous history of rheumatic fever or the presence of inactive rheumatic heart disease.

In no instance was chorea observed, and skin manifestations were rarely noted. Eleven cases, or 19%, gave a history of rheumatic fever, and three of these gave a history of multiple previous attacks. An antecedent upper respiratory infection one to four weeks before admission was recalled by 46, or 79%. Clinically at the time of admission 56, or 97%, were febrile, most in the range of 100 to 102 F, with a few of the more toxic persons running higher spiking fever. Objective evidence of arthritis occurred in all but 2 cases, with polyarthritis in 47, or 81%, while monoarthritis was the finding in 9 cases, or 16%. To emphasize the difficulty in ferreting out malingerers in marching personnel, the knees were involved in 39 cases and the ankles were affected in 33 persons.

Carditis was judged to be present by several criteria [11]: (*a*) the presence of a significant apical systolic murmur, apical middiastolic murmur, or basal diastolic

murmur in a person without a history of previous rheumatic fever or in whom there is a good reason to believe there was no preexisting rheumatic heart disease or a change in the character of any of these murmurs under observation in a person with previous history of rheumatic fever or rheumatic heart disease; (*b*) obviously increasing cardiac enlargement determined by x-ray study; (*c*) pericarditis manifested by a friction rub, pericardial effusion, or definite electrocardiographic evidence; (*d*) congestive heart failure present (in a child or a young adult under 25) in the absence of other causes.

A significant not previously recorded murmur was noted in 11 cases, or 19%. Pericarditis was diagnosed by an audible friction rub in one instance and by ECG changes in six cases. These consisted of elevated ST segments in two cases and inverted T waves in the lateral precordial leads on four occasions. Physical signs of congestive heart failure were noted three times.

Laboratory procedures were extremely helpful in assuring the diagnosis in a number of instances. Due to the early dispersion of patients on other services, some determinations were not made immediately upon admission and some were completely omitted. A leukocytosis with a count of over 10,000 was noted in 27 of 54 cases where tests were performed on admission. Acute-phase reactions were obtained at weekly intervals. The erythrocyte sedimentation rate (Wintrobe) was found to be elevated above 15 mm. per hour in all 58 cases, the average peak being 34 mm. per hour. The C-reactive protein was determined serially in all 58 cases and found to be negative only 4 times. On a 6+ scale its peak elevation was found most often to range between 2+ and 4+.[12,13] An analysis of the C-reactive protein negative cases reveals that in one instance the C-reactive protein was not obtained for one month after admission, the patient manifesting a prolonged P-R interval, elevated antistreptolysin-O titer, past history of acute rheumatic fever, and an organic apical systolic murmur on discharge. Another patient had clinically characteristic acute rheumatic fever and was readmitted after having been discharged from the hospital one day before, the C-reactive protein determination having been omitted during the early acute stage. A Grade 2 apical systolic murmur was present on readmission, presumably in a rebound after cessation of therapy. A third patient was hospitalized on the orthopedic service for 10 days before being transferred to the rheumatic fever ward when the C-reactive protein was first obtained. Nonetheless, approximately one month later a 1+ positive value was recorded. The final patient gave a past history of acute rheumatic fever, along with polyarthritis and intermittent apical systolic murmur.

Evidence of streptococcal infection was derived from both throat cultures and the antistreptolysin-O titer. Throat culture was obtained on admission before antibiotic therapy was instituted in 48 cases, and β-hemolytic Streptococcus was isolated 20 times, or 43% of the cases. Of 28 cases in which β-hemolytic Streptococcus was not isolated, 20 had an antistreptolysin-O titer greater than 200 units. Similarly, of the 10 cases in which a throat culture was not obtained on admission, 7 had an antistreptolysin-O titer greater than 200. Employing all these figures, evidence of recent streptococcal infection can be inferred in 47 cases, or 81%. The antistreptolysin-O titer was

TABLE 2.—*Distribution of Antistreptolysin-O Titers in Fifty-Eight Cases of Acute Rheumatic Fever*

Units/Milliliter	Cases
0	0
100	3
166	4
250	8
333	4
Greater than 333	31
500	1
625	1
Not done	6

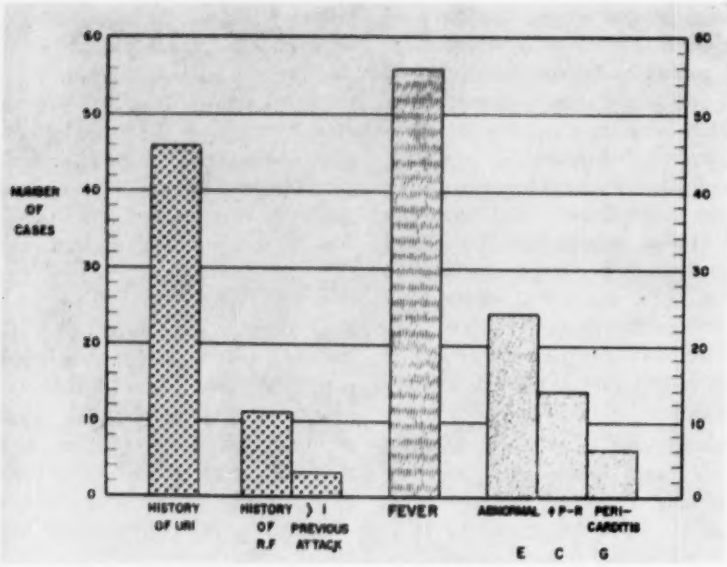
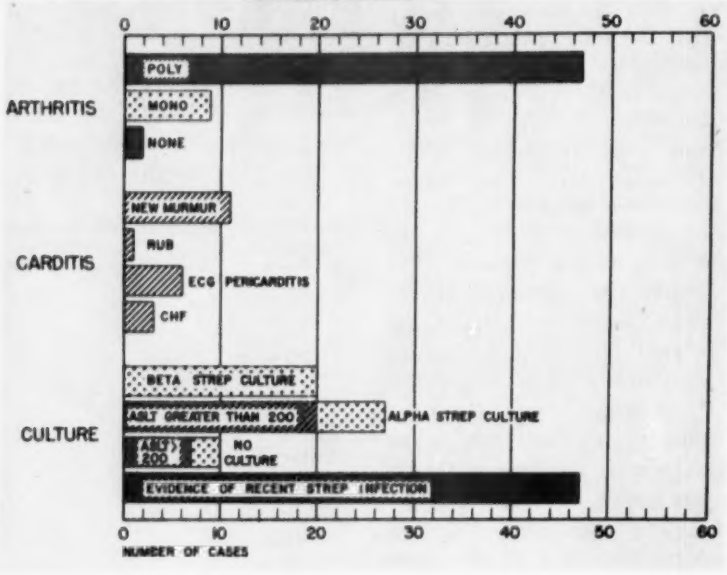


Fig. 3.—Clinical and electrocardiographic findings in 58 cases of acute rheumatic fever.

obtained in 52 cases, of which 45, or 78%, revealed elevations above 200 units.[14,15] The distribution of antistreptolysin-O determinations can be found in Table 2.

Abnormal electrocardiograms were obtained in 24 cases, or 41%, with serial tracings more frequent in the early stages. Prolongation of the P-R interval was most frequently observed, occurring in 14 cases, or 24%. Evidence of pericarditis was documented six times, with elevated ST segments twice and inverted T-waves in the lateral

Fig. 4.—Clinical and laboratory findings in 58 cases of rheumatic fever.



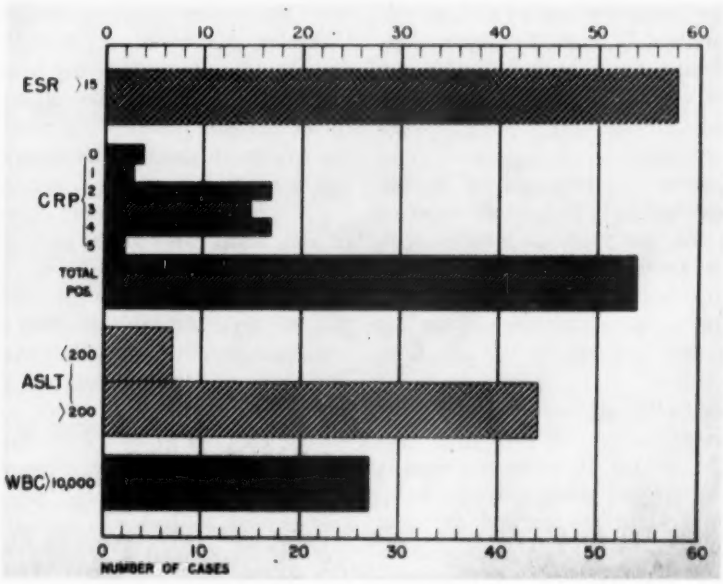


Fig. 5.—Laboratory findings in 58 cases of acute rheumatic fever.

precordial leads in four cases. Prolongation of the Q-T interval and second-degree heart block were seen twice each. Wandering pacemaker and left ventricular hypertrophy were each recorded once. Clinical and laboratory findings are presented in Figures 3, 4, and 5.

Therapy

In order to eradicate persistent and recurrent streptococcal infections, all patients admitted to the rheumatic fever ward were treated with 250,000 units of oral buffered penicillin four times daily for 10 days and thereafter maintained on 250,000 units twice daily throughout the hospitalization. Periodic throat culture surveys were performed to evaluate the adequacy of this program. Recurrent streptococcal infections were encountered twice in the penicillin-protected group and once in a penicillin-allergic person who was maintained on sulfadiazine prophylaxis.

Much attention has been focused recently on the comparison between salicylate, cortisone, and corticotropin (ACTH) therapy of acute rheumatic fever, particularly by the joint United States-United Kingdom survey.[16,17] While the present series admittedly is not large and was not rigidly randomized, certain valid conclusions may be drawn from review of the charts. By and large, the recommendations of McEwen were followed in instituting therapy.[18] When carditis was present on admission, however, both cortisone and salicylates were begun, except for one case where cortisone was the sole therapeutic antirheumatic agent and another in which cortisone therapy was initiated and salicylates added four weeks afterward. Most often therapy was begun with salicylates and cortisone was added when evidence of carditis became manifest. Only in one early instance was no antirheumatic therapy given during the hospital course. Salicylates were employed in the form of the sodium salt in an initial dosage of 10 gm. daily. Salicylate therapy alone was employed in 35 cases, large doses being continued for prolonged periods without premature interruptions to test for activity. Cortisone was the sole therapeutic agent in

one case, and cortisone coupled with salicylates were utilized 21 times. Cortisone maintenance dosage never exceeded 100 mg. daily. The average duration of salicylate therapy and cortisone therapy was 75 and 63 days, respectively.

Much interest has been focused of late on the important interval between onset of symptoms and institution of therapy, with emphasis on a critical period of two weeks.[19] Thirty-two cases in this series were started within three days; forty-three, within the first week, and fifty-one, or 91%, within a two-week period.

Response to therapy as measured by disappearance of fever and joint pain was prompt. In all but three cases salicylate therapy was initiated rather promptly, cortisone being held in reserve and added at some point subsequent to the acute episode. Accordingly, statistics relating to disappearance of fever and joint pain basically reflect the well-appreciated efficacy of salicylates in suppressing the acute phase. In the salicylate-treated group fever abated within 3 days in 26, within 7 days in an additional 14, and within 14 days in another 6. In only two instances did fever persist beyond 14 days while salicylate therapy was given. Similarly, joint pains subsided within 3 days in 18, within 5 days in another 19, and within 14 days in an additional 11. These figures are summarized in Table 3. It will be noted that in no other treatment regimen was a sufficient number of patients started on therapy at the onset, enabling no critical evaluation of the response of the acute manifestations of the disease process.

The average duration of elevation of the erythrocyte sedimentation rate was 35 days, while the average duration for detection of C-reactive protein was 23 days, determinations being made on a weekly basis in most instances. A clinical rebound at cessation of therapy was observed six times, and reappearance of abnormal laboratory findings was noted five times.

An apical systolic murmur heard on admission disappeared at the end of hospitalization four times. The average interval between onset of symptoms and therapy was 9.5 days, and three received salicylates while one was treated with a combination of cortisone and salicylates, cortisone being started some 17 days after salicylates. Among the three patients with apical systolic murmurs at the onset and conclusion of hospitalization the average delay before therapy was 24 days, two receiving salicylates and one, combined therapy. One patient had the murmur of aortic insufficiency at the outset, was given cortisone and salicylates within two days, and was found to have a mitral systolic and diastolic murmur in addition at the conclusion of hospitalization. Eleven patients comprised the group in which a murmur inaudible at the onset was found at disposition. One patient had shortly before been discharged from the hospital with polyarthritis that in retrospect must have represented a mild attack of acute rheumatic fever. Three were treated with salicylates; one, with cortisone, and seven, with the combination. The average delay in therapy was 11.5 days, but eight of these were treated within 5 days. In 15 cases, or 26%, residual murmurs of rheumatic valvular disease were observed, while the remainder were followed for an average of four months. Mitral insufficiency mani-

TABLE 3.—*Effect of Drugs on Disappearance of Acute Manifestations of Rheumatic Fever*

	Fever					Joint Pain				
	None	Within 3 Days	Within 7 Days	Within 14 Days	More than 14 Days	None	Within 3 Days	Within 5 Days	Within 14 Days	More than 14 Days
Salicylates	2	26	14	6	2	--	18	19	11	2
Cortisone	--	1	--	--	1	1	1	--	--	--
Combined therapy	--	3	--	1	--	--	3	1	--	--
No therapy	--	1	1	--	--	1	--	1	--	--

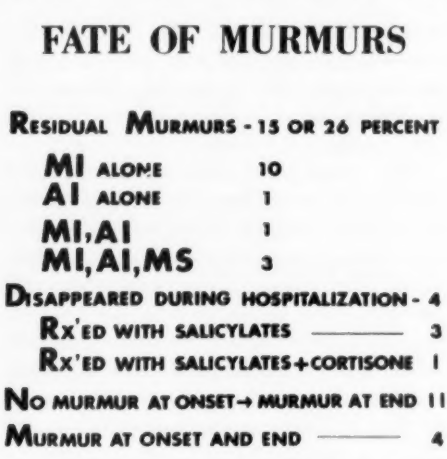

FATE OF MURMURS
RESIDUAL MURMURS - 15 OR 26 PERCENT
MI ALONE 10
AI ALONE 1
MI,AI 1
MI,AI,MS 3
DISAPPEARED DURING HOSPITALIZATION - 4
RX'ED WITH SALICYLATES 3
RX'ED WITH SALICYLATES+CORTISONE 1
NO MURMUR AT ONSET→ MURMUR AT END 11
MURMUR AT ONSET AND END 4

Fig. 6.—Auscultatory findings in epidemic acute rheumatic fever, Parks Air Force Base.

fested by persistent apical systolic murmur alone, occurring 10 times, was the most frequent finding, while aortic insufficiency alone and combined mitral and aortic insufficiency were each observed once. In three instances mitral stenosis and insufficiency along with aortic insufficiency were encountered. A significant murmur absent at the onset was found to be present at the termination of hospitalization in 11 cases, and a persistent murmur was followed through the entire hospital course 4 times (Fig. 6).

The malignant nature of the epidemic is best exemplified by the case of an 18-year-old Negro youth who entered the hospital before the epidemic had been recognized, with high fever, pericarditis with a friction rub, auriculoventricular dissociation, and congestive heart failure. Bilateral pleural effusion was present, and pericardial effusion was suspected by the cardiac contour. No polyarthritis was present, but icterus was noted, along with cylindruria and microscopic hematuria.

Because of denial of joint symptoms, tuberculous pericarditis or an obscure collagen disease were suspected. For approximately 18 days therapy consisted of antibiotics and digitalization. Finally, under cover of antituberculosis chemotherapy, cortisone was begun and effected a dramatic drop in fever. Fifteen days after admission a definite organic apical systolic murmur became audible. Thirty-six days after admission the murmur and circulatory dynamics of aortic insufficiency became manifest, and ninety-five days after admission the murmur of mitral stenosis appeared, all these in spite of continuous cortisone therapy.

Another patient developed acute polyarthritis and was found to have a wandering pacemaker on the initial electrocardiogram. He was observed on bed rest and developed an acute flare-up of joint pain in the hospital. Late in the course of hospitalization, after prolonged salicylate therapy, a significant apical systolic murmur appeared.

Another illustrative patient had a second-degree heart block and persistently inverted T waves on the electrocardiogram. Combined therapy was initiated within 5 days and was continued for 75 days. When a clinical rebound was encountered, therapy was reinstituted for an additional two months, and an organic apical systolic murmur was demonstrable at the conclusion of hospitalization.

Comment

Rapid population increases and overcrowding have been implicated as frequent precursors of respiratory disease epidemics.[20] The clinical course of epidemic acute rheumatic fever has been regularly observed in the military, and the relatively benign nature of the acute episode bears reemphasis. The sporadic disease as seen by the private practitioner seems to present a more complex picture, perhaps because the acute episode may have been suppressed or masked by intermittent inadequate self-medication, bringing the patient under medical care in an advanced stage of the inflammatory process. Perhaps the best early demonstration of the course of acute rheumatic fever unaltered by therapy was made by Graef et al.,[21] in their classic study which included suitable controls. Recent

observations in young adults of the course of acute rheumatic fever modified by drug therapy have been made by the group at the Streptococcal Disease Laboratory at Francis E. Warren Air Force Base, Cheyenne, Wyo.[22]

Several factors were of great interest in the present series. The rapid disappearance of the physical findings following hospitalization and institution of therapy was quite striking. With 56 patients receiving salicylates, fever disappeared within three days in 52% and within one week in 77%. Similarly, joint pain subsided within three days in 38% and within five days in 73%. Thereafter these persons continued on drug therapy and remained hospitalized for a minimum of 3 months, for a total of 7873 man-days. Despite the apparent mildness of the cases and what at the time was considered to be routine accepted drug therapy, 26% proceeded to develop valvular heart disease, sufficient to result in their separation from service by medical board action.

Interesting comparisons may be drawn between the cardiac sequelae of the present series, in the era of steroid therapy, and those recorded in the study of rheumatic fever in the U. S. Army from 1942-1945[23] (Table 4). With the exception of the remarkably high figure of 45% residual apical systolic murmurs reported by Torney General Hospital, in all categories the Parks Air Force Base epidemic equaled or exceeded the Army series. This might further reinforce the concept held by many that steroids have not appreciably altered the inexorable course of rheumatic fever in the past decade.

This series suffers from lack of a control group; but, if conclusions are inadmissable, at least clinical impressions may be formed. The affected group consisted of adult males, 47 of whom were experiencing their first attack of acute rheumatic fever. In the mild uncomplicated case which forms the bulk of the series the acute manifestations melted away under the heavy salicylate dosage, leaving an essentially asymptomatic patient. It is easy to conceive of a person sustaining such an attack in civilian life, self-medicating with acetylsalicylic acid to suppress the acute phase, and proceeding to develop crippling valvular heart disease. Early institution of therapy was the rule, and yet the use of cortisone did not seem to offer any distinct advantages over salicylate. Perhaps larger cortisone dosage for prolonged periods may be a solution, as advocated by Greenman and others.[19,24]

The work of Bland and Jones[25] remains for the present the longest and most complete follow-up of acute rheumatic fever. Carried out in the preantibiotic era, their study indicated that recurrence could be expected in a young rheumatic patient under 20 in 60% to 70% of cases within 10 years of the initial attack. Approximately 25%

TABLE 4.—*Comparison of Epidemic Rheumatic Fever, Parks Air Force Base, with Three General Hospitals, U. S. Army, 1942-1945*

	Parks Air Force Base	Birmingham General Hospital	Foster General Hospital	Torney General Hospital
Apical systolic murmur, %	24.1	11.8	13.0	45.0
Apical diastolic murmur, %	5.2	2.7	8.4	2.5
Aortic insufficiency, %	8.6	10.3	7.7	5.0
Pericarditis, %	10.3	5.6	3.3	3.3
Cardiac insufficiency, %	5.2	0.0	0.6	1.0
ECG				
Any abnormality, %	41.0	53.5	27.7	47.6
Prolonged P-R, %	24.1	26.8	24.6	28.2
Abnormal T waves, %	10.3	10.1	3.1	14.0
Cases, No.	58	262	807	401

of their cases with arthritis had died by 20 years. In the present series those 43 patients without residual heart damage were returned to duty without reservation or restriction. The potential hazards to the patients and the financial liability to the service have been well discussed by Carmichael,[26] who suggested a compulsory reevaluation of such patients after one year. The statistics of Bland and Jones will require review in the light of newer prophylactic measures, which have radically altered expectations of the attack rate of acute rheumatic fever after the exposure to a provocative streptococcal infection. Until more has been learned from investigations now under way to evaluate variables influencing the attack rate, the rheumatic patient will require careful periodic follow-up by trained and interested medical personnel. The patients in the present series were subjected to repeated lectures, on both a group and an individual basis, to educate them regarding current concepts of rheumatic fever and the importance of penicillin prophylaxis as recommended by the American Heart Association.

Summary and Conclusions

An unusual epidemic of 58 cases of acute rheumatic fever in Air Force recruits was experienced at a Northern California basic training center. The epidemologic factors leading to the outbreak were studied, and bacteriologic evidence of elevated streptococcal carrier rates documented. The clinical and laboratory features of epidemic acute rheumatic fever are presented and emphasized. The disease was noted to be generally mild at the onset, and salicylates or combined salicylate and cortisone therapy was begun early. No consistent advantage could be found for the regimen including cortisone. Twenty-six per cent of the cases exhibited residual valvular damage at the conclusion. Comparisons have been drawn between this epidemic and the disease as experienced during World War II, when steroids were not available. Some implications of the disposition of patients with acute rheumatic fever in the military are mentioned.

Col. William Carpenter, Base Commander; Col. Frank Lane, Base Surgeon, and Col. William Look, Chief of Professional Services, cooperated in this study. Assistance was provided by Capt. Carl Spaur, Laboratory Officer, and the members of the laboratory staff of the 3275th U. S. A. F. Hospital, in particular those assigned to the Serology and Bacteriology Sections: Mr. Donald Lamanna, Mr. Sam Chitjian, A/1C Robert W. Bolding, A/1C William A. Alston, A/1C Donald F. Miller, and S/Sgt. Mary E. Revels, all of whom performed an assignment superimposed upon their routine laboratory duties. Mrs. Marian Hotchkiss, Mrs. Shirley Ellenwood, and Mrs. Wynnefred Parker typed the manuscript. Encouragement and advice was given by Major Max Nareff, Chief, Cardiovascular Disease Section. Dr. Charles Hudson, Medical Consultant, of Oakland, Calif., participated regularly in the task of evaluating murmurs.

3550 Pine Grove Ave., Chicago 13.

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II. Prophylaxis with Tandem Oral Penicillin

CAPT. HAROLD P. LAZAR (MC); CAPT. GERALD I. MAAS (MC); CAPT. WALTER HARRISON (MSC); COL. JAMES H. HAMMOND (MC), U.S.A.F., Parks Air Force Base, Calif., and LOWELL A. RANTZ, M.D., San Francisco

The efficacy of penicillin in the prevention of streptococcal infections and rheumatic fever is a well-documented fact.[1-4] Exposure of large numbers of service recruits to virulent streptococci has been followed by massive outbreaks of epidemic acute rheu-

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From the Department of Medicine and the Streptococcal Disease Control Board, 3275th U. S. A. F. Hospital, Parks Air Force Base, Calif., and the Department of Medicine, Stanford University School of Medicine, San Francisco. Aided by Grant No. H 700 from the National Heart Institute, National Institutes of Health.

Streptococcal Disease Control Coordinator; now at Michael Reese Hospital, Chicago; present address, 3550 Pine Grove Ave., Chicago 13, (Capt. Lazar). Member, Streptococcal Disease Control Board, (Capt. Maas). Administrative Sanitary Officer (Capt. Harrison). Chief, Department of Medicine, and Streptococcal Disease Control Officer (Col. Hammond). Professor of Medicine, Stanford University School of Medicine, and Consultant, 3275th U. S. A. F. Hospital, Parks Air Force Base, Calif. (Dr. Rantz).

matic fever with its attendant serious cardiac sequelae.[5] A previous report recounted the epidemiology and clinical picture of epidemic acute rheumatic fever as it was experienced in the first half of 1955 at a large Air Force basic training center in Northern California.[6] It is the purpose of this paper to relate and discuss an approach to the practical aspects of streptococcal disease and rheumatic fever prevention, with particular reference to a tandem oral penicillin method of prophylaxis.

Background

While rheumatic fever attack rates are notoriously inaccurate, Northern California has never been noted as a particularly vulnerable area. When, however, 58 well-documented cases of acute rheumatic fever were accumulated in a six-month period beginning Jan. 1, 1955, in a large basic training center, the morbidity was established to be 4.1 per 1000 per annum, a figure approximately four times the Air Force-wide rate for 1951. Careful epidemiologic investigations revealed the presence of a strikingly elevated streptococcal carrier rate in recruits who had spent 60 days on the base, half of whom harbored β-hemolytic streptococci in their upper respiratory tracts. A base-wide oral penicillin prophylaxis program lasting 10 days, late in the respiratory disease season and utilizing a tested regimen, was instrumental in aborting the tail of the epidemic. Fifteen patients, 26% of the series, suffered residual rheumatic valvular damage sufficient to result in separation from military service. As a direct consequence of experiences with this outbreak, plans were formulated and set into action to avert a repetition during the following respiratory disease season.

Organization of the Program

When the need for efficient administrative control was so strongly recognized, a Streptococcal Disease Control Officer, in this instance the Chief of Medicine, was delegated to preside over a control board whose functions were clearly defined. Members of the board included the ward officers in charge of the upper respiratory disease ward and the contagion ward, as well as the Chief of the Cardiovascular Disease Section. In addition, the laboratory officer was designated to assist in providing prompt bacteriologic data, and the Administrative Sanitary Officer was assigned as liaison officer with the basic training group to act in procurement and distribution of penicillin tablets for prophylaxis. Finally, a medical officer was appointed to coordinate the activities of the board with the dispensaries and training personnel and to collect and screen all data relevant to the program. In conjunction with the medical efforts a basewide education program was organized to emphasize the need for prompt and adequate therapy directed at sore throats, according to the recommendation of the American Heart Association.

The cooperation of the dispensary physicians was sought and obtained so that the trend of streptococcal disease might be followed in the basic training population. Each person presenting himself at his dispensary with the complaint of sore throat was subjected to a throat culture before the institution of appropriate antibiotic therapy, and, unless the diagnosis of streptococcic sore throat were clinically obvious, symptomatic therapy alone was prescribed prior to obtaining the throat culture report. Definite criteria were established for admission to the upper respiratory disease ward: An oral temperature of 100 F in association with an exudative pharyngitis or tonsillitis. These criteria had to be streamlined and simplified in consideration for physicians of varying specialty backgrounds who might encounter such patients in the hospital emergency room during night or weekend duty. Precise rates for streptococcal and nonstreptococcal upper respiratory disease were derived from hospital discharge diagnoses, assuring bacteriologically proved diagnoses. Finally, a search for reservoirs on the base was undertaken by the coordinator, who cultured representative samplings of technical instructors and mess hall personnel but found negligible numbers of streptococcal carriers.

Results

Begun on a small scale in October, 1955, the control program was in full operation by Nov. 1. On Dec. 9, 1955, a conference to assess the accumulated data revealed that eight rheumatic fever suspects had been admitted since Nov. 1. In addition, the bacteriologic surveys conducted in the dispensaries revealed that in the preceding five-week period 186 of 581 throat cultures, or 32%, were found to yield β-hemolytic Streptococcus. An increase in the basic training population at that point was accompanied by an upsurge in the streptococcic sore throat hospital admission rate to a level of 3.7 per 1000 per week. Accordingly, on

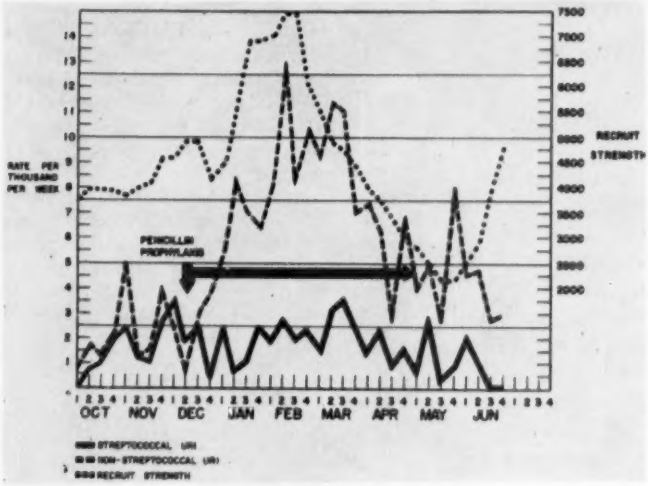
Dec. 14, 1955, all recruits were started on a program of 250,000 units of oral buffered crystalline penicillin G, administered (by training instructors) when the stomach was empty twice daily for 10 days. From that point on, in tandem fashion, all recruits upon reaching the 14th day of residence on the base were begun on a similar prophylactic program. This regimen was maintained until May 1, 1956, an arbitrarily designated cut-off date, by which time some 25,305 recruits had been included in the program. Any recruit with a plausible history of penicillin allergy was excused from participation in the program. No serious allergic responses were encountered. In response to this use of penicillin, the number of β-hemolytic streptococcal isolations in the dispensary throat culture program fell sharply and was maintained at a level below 5%, approximately one-sixth its initial level. Owing to limitations in available funds and personnel, consistent streptococcal typing was not possible. Typing performed in December, January, and May by the Sixth Army Medical Laboratory at Fort Baker, Calif., revealed no reaction with 23 available typing sera. Cultures submitted in April, 1956, revealed the presence of Types 6 and 12.

On examination of the Figure it is readily apparent that the streptococcal disease admission rate was consistently maintained between 1 and 3 per 1000 per week, despite a doubling of the basic training population by February, by which time a peak nonstreptococcal upper respiratory disease rate of 13 per 1000 per week had been attained, presumably ARD.

That the primary objective of the program was attained is attested to by the fact that only seven cases of acute rheumatic fever were encountered from Jan. 1 to July 1, 1956. An analysis of these cases revealed that one person presented himself with acute rheumatic fever just two days after arriving from his previous station, Sampson Air Force Base. Two patients were not basic trainees but were assigned to the Air Base Defense School, an organization not included in the prophylactic program. One patient apparently acquired his streptococcal infection very early, since he was admitted with acute rheumatic fever on the second day of his prophylactic regimen. Another patient admitted avoiding taking his tablets, stating that he took a total of three or four in sporadic fashion. Another was noted to have the murmur of aortic insufficiency on the fourth hospital day, raising some question about the diagnosis of acute rheumatic fever in the present episode. The final patient developed acute rheumatic fever five weeks following his course of prophylactic penicillin, an occurrence perfectly consistent with the expected duration of protection afforded by orally administered penicillin.[3]

Several additional factors must be taken into consideration. At the height of the respiratory disease epidemic it became common practice to administer 1,200,000 units of benzathine penicillin to those persons with bacteriologically demonstrated β-hemolytic streptococcic sore throats on discharge from the hospital if hospitalization were under 10 days, in order to insure penicillin blood levels for 10 days. This undoubtedly diminished the possibilities for reinfection of the barracks population by these persons. In addition, in the midst of the study there was a change in the organization of the basic training program in that some recruits were hastened through their curriculum and shipped to technical schools within as short a period as four weeks. This reduced the effective period of observation and follow-up and made necessary inquiries to other Air Force hospitals.

Inquiries were directed to those secondary bases receiving the recruits at the completion of the first phase of their basic training at Parks Air Force Base. Complete lists of rheumatic fever admissions for the first six months of 1956 were obtained, and these names were cross checked against the files of the basic training organization at Parks Air Force Base. With the aid of data from those bases receiving 93% of the men shipped for technical training, it has been ascertained that only eight admissions for acute rheumatic fever occurred among men who



Relationship of streptococcal and nonstreptococcal respiratory disease rates to recruit strength and penicillin prophylaxis, Parks Air Force Base, October, 1955-June, 1956.

had their basic training at Parks Air Force Base during the period the prophylaxis program was in effect. With the exception of one man who developed acute rheumatic fever eight days after arriving at his secondary base, all developed signs and symptoms of acute rheumatic fever at least 4 to 12 weeks from the time of departure from Parks Air Force Base. This would tend to suggest that the provocative streptococcal infection was not acquired at Parks Air Force Base. Unfortunately interviews were not possible to ascertain whether the recruits faithfully adhered to the prophylaxis program during their basic training.

Comment

Much effort has been expended by the military to ascertain the cheapest, most practical, and most effective method of achieving prevention of streptococcal disease and rheumatic fever. The earliest efforts centered about the use of sulfonamides, resulting in the emergence of sulfonamide-resistant strains of β-hemolytic Streptococcus.[5] With the advent of penicillin, more effective control became possible, but the problem of route of administration soon achieved prominence. The earliest reports of Wannamaker et al.[2] related to the use of a larger oral dosage than is customary at present, and subsequent investigations conducted by the Navy were directed toward determining the optimum dosage and duration of administration.[7] For ease of administration, economy, and duration of protection, a 10-day course such as that employed in this study has been recommended and used successfully on several occasions.[3,4]

Previous investigators have preferred sporadic base-wide bursts of prophylaxis to continuous programs. The aim in this project was to protect each man at the time of increasing risk of acquisition of the streptococcal carrier state.

Several questions are still to be answered regarding the operation of such a program. Despite the fact that the tablets were doled out singly and presumably their ingestion monitored by training instructors, there remains room for skepticism regarding this phase. Only the most naive person could assume that rigid control could be exercised over administration of penicillin under such circumstances. Allowing for such abuses, one must concede that this tandem scheme has been remarkably effective.

Methods to circumvent these administrative problems have been considered and implemented. Intramuscular benzathine penicillin has been employed in a dosage

of 1,200,000 units by the Navy with excellent results, eliminating all question of producing adequate blood levels for 10 days.[8] Penicillin allergy has been studied at Warren Air Force Base, and the investigation compared reactions to 1,200,000 units of intramuscular benzathine penicillin, 600,000 units of intramuscular benzathine penicillin, and oral penicillin in the dosage of 250,000 units twice daily for 10 days. Allergic responses were noted to fall in the ratio of 5:2:1.[9] Stollerman has found benzathine penicillin to be no more allergenic,[10] and the U. S. P. H. S. has encountered remarkably few reactions with benzathine penicillin in venereal disease programs.[11] Despite the claims of the proponents of benzathine penicillin prophylaxis, other investigators have been reluctant to employ benzathine penicillin on a large scale, owing to concern over the presumably elevated reaction rate. Perhaps further studies might be undertaken to assess the efficacy and shortcomings of intramuscular benzathine penicillin in a large recruit population such as ours. This would seem to follow logically as the next step in the sequence of these investigations.

Conclusions

Epidemic streptococcal disease and acute rheumatic fever have been effectively controlled in a large Northern California U. S. A. F. basic training center by means of a tandem oral penicillin prophylaxis program involving 25,305 recruits during the respiratory disease season.

Strict bacteriologic surveys are extremely valuable in heralding outbreaks of streptococcal disease. Conceivably, complete elimination of acute rheumatic fever is possible with an adequately implemented tandem program. Defects in the system are discussed, and a trial of tandem intramuscular benzathine penicillin is suggested.

Major Gen. James W. Spry, Base Commander; Col. Frank Lane, Base Surgeon; Col. William Look, and Col. John W. Linfesty, Chiefs of Professional Services, cooperated in this study. Assistance was provided by Capt. Carl Spaur, Laboratory Officer, and the members of the laboratory staff of the 3275th U. S. A. F. Hospital, in particular those assigned to the Bacteriology Section: Mr. Sam Chitjian, Supervisor; A/1C Vaisigago Uperesa; A/1C Robert W. Bolding; A/1C John W. Grof, and A/2C John B. Nash, all of whom performed an assignment superimposed upon their routine laboratory duties. Mrs. Marian Hotchkiss and Mrs. Shirley Ellenwood typed the manuscript. This study would not have been possible without the assistance of the entire body of medical officers assigned to the base, especially those physicians of the department of medicine: Major Nester M. Hensler, Major Max J. Nareff, Major Robert H. Worthman, Capt. Leo J. Rain, Capt. Harry E. Hill, and Capt. Paul F. Flynn.

3550 Pine Grove Ave., Chicago 13.

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Membranous Glomerulonephritis

ALVIN E. PARRISH, M.D.; MARY F. WATT, M.D., and JOHN S. HOWE, M.D., Washington, D. C.

Membranous glomerulonephritis has been recognized as a pathological entity since it was described by Bell,[1] and both he and others [2] have considered it closely related to acute glomerulonephritis. Ellis [3] suggested that acute glomerulonephritis might appear initially in more than one form. His "Type I" nephritis included the usually recognized clinical picture of acute glomerulonephritis with hypertension, azotemia, hematuria, proteinuria, and edema, and his "Type II" nephritis fits the clinical and pathological picture of membranous glomerulonephritis with massive proteinuria and anasarca. This form of glomerulonephritis has frequently been described as a separate entity, lipoid nephrosis.[4] However, lipoid nephrosis fits the pathological criteria for membranous glomerulonephritis [1,3] and is both histologically and functionally predominantly a glomerulitis.[5]

Renal needle biopsy has allowed premortem microscopic examination of the kidney and has led to the recognition of membranous glomerulonephritis in the adult. Nine instances of the entity have been encountered during the past five years and form the basis for this report.

Methods

Renal needle biopsy was performed in patients with the nephrotic syndrome, with use of the technique previously described.[6] Renal functions were determined by using inulin clearance to estimate glomerular filtration rate (GFR), sodium *p*-aminohippurate (PAH) clearance to measure effective renal plasma flow (ERPF), and the Tm_{PAH} to measure tubular function. Paper electrophoretic studies of serum and urinary protein were carried out in some patients, with use of a Spinco electrophoresis cell. Urinary protein was concentrated by dialyzing against polyvinylpyrrolidone (Plasdone).[7] These patterns were plotted with a Spinco recording scanner and integrator.

CASE 1.—A 45-year-old white male construction engineer was admitted with a history of ankle edema, cloudy urine, and proteinuria for seven days. He had had cystitis two years previously and had been discharged from the Army Reserve Corps because of high blood pressure. During the two years before his present illness his blood pressure had varied in the range of 140-150/80-90 mm. Hg. One month before his present illness he had had hepatitis with jaundice, fever, and anorexia which cleared over a period of days. There was no history of exposure to toxic materials.

On admission physical examination revealed normal temperature and pulse; blood pressure, 140/82 mm. Hg, and weight, 190 lb. A soft systolic murmur was heard over the pulmonic area, and there was periorbital and ankle edema.

The initial laboratory studies showed a normal hematocrit reading, blood cell count, N. P. N., P. S. P. excretion, and liver functions. Marked proteinuria was present, with hypoproteinemia, reversal of the A/G ratio, and hypercholesterolemia. Urea clearance was 51% of standard clearance, and an Addis count showed abnormal numbers of RBC, WBC, and casts. Findings on renal biopsy were interpreted as acute membranous glomerulonephritis (Fig. 1*A*). This showed slight thickening of the glomerular basement membrane and capsular membrane. Glomeruli were less vascular than normal, and there was slight proliferation of the glomerular epithelium.

During hospitalization he gradually improved with no specific therapy, and, although proteinuria and hypoproteinemia persisted, his edema disappeared and he was discharged. Two weeks after discharge his edema recurred and rapidly progressed to anasarca. He was admitted to the George Washington University Hospital, where, after a stormy course during which he developed a myocardial infarct, he died, approximately eight months from the onset of his disease. At autopsy his kidneys were found to be large, pale, and

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From the Departments of Medicine and Pathology, Veterans' Administration Hospital and the George Washington University. Research Fellow, National Institute of Arthritis and Metabolic Diseases (Dr. Watt).

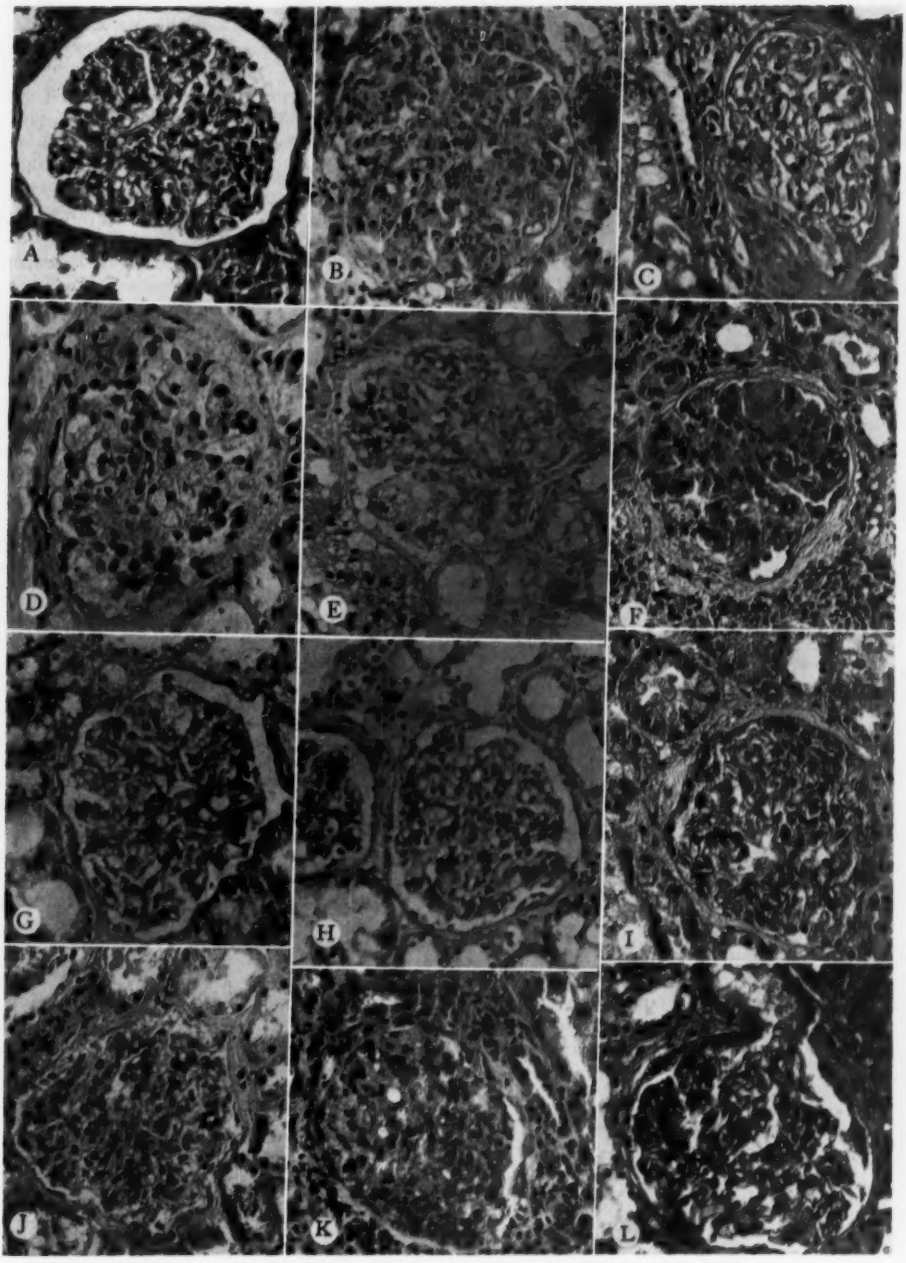

Fig. 1.—Pathology seen in acute membranous glomerulonephritis. *A* and *G*, Case 1. *J* and *D*, Case 2. *B*, *E*, and *H*, Case 3. *K*, *F*, and *C*, Case 4. *I* and *L*, Case 5.

smooth. The left kidney weighed 250 gm., and the right, 220 gm. Microscopic examination of the kidneys (Fig. 1*G*) revealed all of the glomeruli to be involved by changes which were more marked than those seen at the time of biopsy. These consisted of a diffusely thickened eosinophilic basement membrane, with some narrowing of the lumens of capillary loops. Some of the glomeruli showed a simplification of their structure, with transformation into four or five acidophilic lobules. This represented a progression of the lesion from pure membranous glomerulonephritis in the biopsy specimen to membranous and lobular glomerulonephritis at the time of autopsy.

CASE 2.—A 41-year-old white male office worker was admitted with a history of generalized weakness and edema of his legs and nocturia of two weeks' duration. He had a past history of a back injury 10 years prior to admission but never had symptoms of renal disease.

Physical examination revealed normal blood pressure, pulse, and temperature. There was a small amount of ascites and 4+ pitting edema up to the knees.

The initial white cell count was elevated to 17,600, with a normal differential count. The hematocrit reading was 52%. Blood urea nitrogen, creatinine, nonprotein nitrogen, and serum sodium and potassium were normal. Serum total proteins ranged from 5.0-6.8 gm/100 ml., with serum albumin ranging from 3.1-4.0 gm/100 ml. Urea clearance was 34% of maximum clearance, and P. S. P. excretion was 15% in 15 minutes. The blood cholesterol was 368 mg/100 ml. The urine contained 14 gm. of protein per 24 hours, and there was a low specific gravity, of 1.003. The urinary sediment revealed many oval fat bodies and fatty casts. Chest x-ray, intravenous pyelogram, and ECG were normal. Findings on renal biopsy were interpreted as showing acute membranous glomerulonephritis (Fig. 1*J*). The glomeruli were moderately cellular and showed synechia formation, thickening of the basement membrane, and decreased vascularity. The tubules were dilated, and the epithelium was vacuolated.

He was given cortisone, 400 mg. daily, and lost 30-40 lb. of weight over a period of several days. He showed gradual improvement, with loss of edema and a decrease in proteinuria and was discharged after two months on a regimen of 100 mg. of cortisone daily. A second renal biopsy (Figure 1*D*) was performed before discharge, and this showed continued increased glomerular cellularity and decreased vascularity. The tufts were adherent to each other and to the capsule. The tubules were dilated and showed coarse vacuolization of their epithelium.

After discharge he remained well for four months. The cortisone dosage was gradually reduced to 50 mg. per day. At this time he developed melena and was readmitted with a bleeding duodenal ulcer. Laboratory studies and physical examination revealed no evidence of renal disease. Urine findings were negative for protein and abnormal sediment. Cortisone therapy was discontinued, and after discharge he remained well except for nocturia and occasional proteinuria. Ten months from the onset of his disease his P. S. P. excretion was 30% in 15 minutes; urea clearance, 63% of standard clearance; B. U. N. 11 mg/100 ml.; serum protein, 7.3 gm/100 ml.

One year later he was readmitted for further examination. Renal functions (Table 1) at this time were normal except for some depression of the Tm_{PAH} (49 mg. per minute). Findings on renal biopsy were essentially the same as on the previous biopsy.

CASE 3.—A 43-year-old Negro laborer was in good health until four weeks prior to admission, when he developed a "cold" and nonproductive

TABLE 1.—*Renal Functions* *

Case	Date	Inulin Clearance, Ml./Min.	PAH Clearance, Ml./Min.	Tm_{PAH} Mg./Min.	In/PAH	In/Tm_{PAH}	PAH/Tm_{PAH}
4	3/19/56	54	401	21	0.14	2.57	19.1
	4/12/56	40	278	30	0.14	1.33	9.3
	7/25/56	44	350	13	0.12	3.33	26.5
3	2/21/55	91	657	108	0.16	0.84	6.1
	3/31/55	128	506	49	0.25	2.61	10.3
	10/18/55	95	372	96	0.26	0.99	3.9
2	12/ 1/55	155	524	49	0.30	3.16	10.7
5	11/ 1/56	98	625	70	0.16	1.39	8.9
	12/ 3/56	110	631	79	0.17	1.39	8.0
6	12/17/53	72	464	104	0.15	0.69	4.4
Range		40-155	278-657	13-108	0.12-0.30	0.69-3.33	3.92-6.5

* All values corrected to a surface area of 1.73 sq. m.

cough. One week later he noted a swollen abdomen, back pain, and dark red urine. A week before admission to the hospital his legs, genitalia, and face became swollen.

Examination showed a blood pressure of 150/100 mm. Hg and normal pulse and temperature. There were a few rales in his left lung field posteriorly. Ascites was present, and there was edema of his penis, scrotum, sacrum, and extremities.

Initial laboratory tests revealed a normal blood cell count. The urine showed a specific gravity of 1.016, 4+ albumin, 10-20 RBC, and many fatty casts and oval fat bodies. The 24-hour urinary protein was 13 gm., and the blood protein, 5.5 gm/100 ml., with 3.4 gm. of albumin and 2.1 gm. of globulin. Blood urea nitrogen was 38 mg/100 ml.; creatinine, 2.8 mg/100 ml.; cholesterol, 161 mg/100 ml.

He was given cortisone, 400 mg. per day, and over the course of four months he gradually lost the edema and proteinuria. The blood urea nitrogen value returned to normal by the 23d hospital day. The urinary sediment showed showers of RBC up to the time of discharge. The blood protein level remained low (5.5-5.7 gm/100 ml.) until after discharge.

On his sixth hospital day a renal biopsy was performed, which showed acute glomerulonephritis (Fig. 1*B*). The glomeruli were large, filling the capsular space, with some adhesions to the capsule. The glomerular basement membrane was thickened, and both endothelial and epithelial cells were proliferating. There were numerous polymorphonuclear leukocytes in the basement membrane. The vascularity of the glomeruli appeared to be reduced. After a month, however, a repeat biopsy was more compatible with acute membranous glomerulonephritis (Fig. 1*E*). This showed increased thickening of the basement membrane and increased cellularity, with a loss of the polymorphonuclear infiltration and decreased vascularity when compared with the findings on the initial biopsy.

Renal functions (Table 1) at the time of the first biopsy revealed minimal impairment of glomerular filtration (91 ml. per minute) and a high Tm_{PAH} (108 mg. per minute). After one month the glomerular filtration rate was normal, but there was a fall in Tm_{PAH} (49 mg. per minute).

After discharge from the hospital he continued to complain of malaise, bilateral lower quadrant pain, dysuria, frequency, nocturia, and a weight gain of 26 lb. He returned to the hospital with these symptoms three months from the time of discharge. Physical examination was normal. Laboratory tests were normal except for minimal proteinuria (0.32 gm/24 hours) and a total cholesterol value of 304 mg/100 cc. A repeat renal biopsy still revealed membranous glomerulonephritis (Fig. 1*H*). The increased cellularity and thickening of the glomerular basement membrane persisted, and there was little change from the findings on the previous biopsy. Renal functions at this time are shown in Table 2. He was discharged after two weeks and since that time has been asymptomatic. His urine has cleared; he has had no edema, and he has returned to work as a laborer.

CASE 4.—A 34-year-old Negro laborer was admitted to another hospital with a chief complaint of swelling of his face and feet beginning one week before admission. One week earlier he had had a "cold" without fever or sore throat.

Examination was normal except for blood pressure of 140/90 and edema of the face and legs.

Laboratory studies, including a blood cell count and blood urea nitrogen value, were normal. Urinalysis revealed 4+ proteinuria and occasional WBC, RBC, and granular casts. X-rays and ECG's were normal. A throat culture was positive for β-hemolytic streptococci.

During the first week of hospitalization the edema disappeared; however, the urine continued to contain protein, and the total blood protein value fell. A blood cholesterol value was 644 mg/100 ml. He was discharged with the diagnosis of chronic glomerulonephritis after two months.

Two months later he was admitted to the Veterans' Administration Hospital in Washington, D. C., with a recurrence of edema, which by the time of admission had progressed to generalized anasarca and ascites.

TABLE 2.—*Serum and Urinary Protein Partition*

Case		Total	Albumin, %	α_1-Globulin, %	α_2-Globulin, %	β-Globulin, %	γ-Globulin, %
4	Serum	3.63 gm./100 ml.	14.5	4.5	59.0	20.2	8.9
	Urine	22.6 gm./24 hr.	52.2	18.0	8.1	12.1	9.6
5	Serum	3.25 gm./100 ml.	27.5	10.5	35.9	19.3	7.0
	Urine	5.9 gm./24 hr.	54.6	13.7	9.8	16.9	5.1

Examination showed a blood pressure of 140/96 mm. Hg, a normal pulse and temperature, ascites, and generalized edema.

Laboratory tests revealed a normal blood cell count and grossly abnormal urine with specific gravity of 1.019, proteinuria of 4+, many nucleated cells, and casts of all types. Oval fat bodies and fatty casts were abundant. Blood urea nitrogen was 37 mg/100 ml., and total serum protein was 4.6 gm/100 ml. Serum cholesterol was 600 mg/100 ml.; serum sodium, 126 mEq. per liter; serum potassium, 5.0 mEq. per liter; C-reactive protein, negative; I^{131} uptake, normal. An initial renal biopsy showed (Fig. 1*K*) moderate thickening of the basement membrane, with some increase in cellularity and avascularity. The proximal convoluted tubules had swollen finely and coarsely vacuolated cytoplasm. There was slight infiltration of the interstitial tissue by round cells. This was considered compatible with acute membranous glomerulonephritis.

Renal function studies done at this time (Table 1) revealed a decrease in all functions.

He was given prednisone (Meticorten) (30 mg. daily), then cortisone (400 mg. daily), without effect. Albumin was then given intravenously with a good diuretic effect. His weight fell from 174 lb. to a low of 132 lb. Proteinuria persisted in large amounts (20-25 gm. per day). Serum and urinary electrophoretic patterns (Table 2) were abnormal, with a marked decrease in serum albumin and increase in α_2-globulin. These have remained unchanged throughout his hospital course when studied at weekly intervals.

A repeat renal biopsy two weeks later revealed no change in the pathological picture. After two and one-half months there was a progression of the pathology (Fig. 1*F*). The glomeruli showed changes varying from marked thickening of the basement membrane to the formation of hyalinized lobules and stages of sclerosis with almost complete avascularity and the formation of synechiae. Severe atrophy of the tubules was present, with marked interstitial fibrosis and infiltration with plasma cells and polymorphonuclear leukocytes. Better-preserved tubules showed coarse vacuolization. Some of the atrophic tubules were lined with flattened epithelium and filled with protein casts.

After five months (Fig. 1*C*) these changes had progressed to those consistent with a lobular and sclerosing stage of membranous glomerulonephritis.

The renal functions (Table 1) demonstrated progressive deterioration. Proteinuria has persisted up to the present time, varying between 15 and 25 gm/24 hours. The serum protein value remains low (2-3 gm/100 ml.) and the blood urea nitrogen remains slightly elevated (25-35 mg/100 ml.). In spite of this he has shown clinical improvement, with a loss of his edema and return of appetite.

TABLE 3.—*Summary of Pertinent Findings*

Case	Age	Clinical: Onset	Clinical: Edema	Clinical: B.P., Mm. Hg	Blood: Cholesterol, Mg./100 Ml.	Blood: Total Protein, Gm./100 Ml.	Blood: Albumin Globulin	Blood: B.U.N., Mg./100 Ml.	Blood: Hematocrit, %	Urine: Protein, Gm./24 Hr.	Urine: Fat: Cells	Urine: Fat: Casts	Urine: RBC: Cells	Urine: RBC: Casts	Urine: P.S.P.*	Urea Clearance†	Specific Gravity
Acute																	
1	45	Insidious?	4+	140/82	720	5.0	2.5 2.5	44	43	16.8	+	+	+	0	25	81	1.017
2	41	2 wk. before admission	4+	115/80	368	6.75	3.5 3.2	20	49	14.1	+	+	0	0	15	34	1.018
3	43	4 wk. before admission	2+	150/100	304	5.5	3.4 2.1	38	41	9.8	+	+	+	0	25	50	1.020
4	34	2 wk. before admission	4+	140/90	644	4.6	1.8 3.3	65	35	20.0	+	+	+	0	5	24	1.008
5	34	5 days before admission	4+	130/80	540	3.2	0.9 2.3	29	31	5.9	+	+	+	0	35	118	1.024
Chronic																	
9	55	Insidious?	0	120/90	---	6.15	3.9 2.2	14	49	4.0	0	0	+	0	15	--	1.030
6	63	? 2 yr. before admission	4+	190/100	450	5.0	2.0 3.0	32	47	8.5	+	0	+	0	10	48	1.025
7	46	? 8 yr. before admission	0	140/82	296	6.6	4.5 2.0	18	48	2.8	+	0	0	0	20	72	1.008
8	36	2 yr. before admission	+	140/120	154	6.0	2.8 3.1	26	47	0.6	0	0	+	0	20	56	1.015

* % excretion in 15 minutes.
† % normal clearance.

CASE 5.—A 34-year-old white male aircraft machinist was well until six to seven weeks before admission, when he noted anorexia, weakness, and easy fatigability. Five days before admission he developed nausea, vomiting, diarrhea, and ankle edema. His edema increased up to the time of admission. He had had no prior history of renal disease or scarlet fever. His son was treated for acute glomerulonephritis three months previously.

Examination was normal, with blood pressure, 138/80; pulse, 88; temperature, 98.6 F, except for ascites and pitting edema of his legs and sacral area. His initial laboratory data showed a normal blood cell count, blood urea nitrogen, 39 mg/100 ml.; serum creatinine, 0.9 mg/100 ml.; total protein, 3.6 gm/100 ml.; cholesterol, 540 mg/100 ml.; serum potassium, 6.0 mEq. per liter, and sodium, 130 mEq. per liter. The urine contained 4+ protein, with many hyalin and granular casts and epithelial cells. Sudan-III-staining fat and doubly refractile bodies were present. Serum and urine protein electrophoretic patterns are shown in Table 2. A summary of the pertinent findings are shown in Table 3. A renal biopsy (Fig. 1*I*) revealed diffuse thickening of the basement membrane, a slight increase in cellularity of the glomeruli, and coarse vacuolization of the tubular epithelium. This was compatible with membranous glomerulonephritis. Renal functions (Table 1) were normal.

He was given cortisone, 400 mg. per day for 10 days. During this period he showed no improvement, and there was a weight gain of 26 lb. When cortisone was stopped there was a prompt diuresis, with the urine volume reaching 8000 ml/24 hours, and a weight loss of 51 lb. Urine protein fell from 5.9 gm/24 hours to 1.5 gm/24 hours, and there was a rise in serum protein to 5.6 gm/100 ml. A repeat renal biopsy (Fig. 1*L*) after one month showed findings similar to the first but with some decrease in the glomerular cellularity. Renal functions again were normal (Table 1).

After 38 days of hospitalization he was discharged, asymptomatic, free of edema, and with only a trace of protein in his urine.

Comment.—These five patients represented a disease with a gradual onset in two and an onset similar to acute glomerulonephritis in three. Four of the five could date the onset of their illness, and the initial manifestation was edema. All eventually presented a picture of a nephrotic syndrome, with edema, hypoproteinemia, proteinuria, hypercholesterolemia, and fatty casts and oval fat bodies in their urinary sediment. Hypertension was not usual, and RBC casts were not found. The pertinent data are presented in Table 3. Findings on renal biopsy in one initially were compatible with acute glomerulonephritis, but in all five after a month of illness biopsies revealed changes compatible with membranous glomerulonephritis. These changes were primarily thickening of the glomerular basement membrane, with some increase in the cellularity of the glomeruli. Follow-up biopsies demonstrated persistence of basement-membrane swelling for one month in Case 5 and for 14 to 20 months in Cases 2 and 3, even though the patients at the time of the last biopsy were asymptomatic. In two other patients the lesion progressed to a picture of lobular glomerulonephritis (Cases 1 and 4).

Renal functions improved (Table 1), but never, even after a year in Case 3, returned completely to normal and have become progressively worse in Case 4. Renal functions in Case 5 have been normal.

The diagnosis could be suspected in these patients from the lack of a previous history of renal disease, with a rapid onset of a nephrotic syndrome. Renal biopsy served to differentiate other diseases giving rise to the nephrotic syndrome, such as amyloidosis, lupus erythematosus, interstitial glomerulosclerosis (Kimmelstiel-Wilson syndrome), and chronic glomerulonephritis.

The following four cases all revealed the unexpected finding of membranous glomerulonephritis.

CASE 6.—A 63-year-old male clerk was admitted because of a two-week history of progressive swelling of his legs, genitalia, and abdomen. He had had an abdominal perineal resection for carcinoma of the rectum six years before and a subtotal gastrectomy for a bleeding duodenal ulcer two years previously. On this latter admission minimal proteinuria was noted.

Examination showed a blood pressure of 190/100 mm. Hg, a colostomy, ascites, edema of the legs and genitalia, and hepatomegaly. Laboratory tests were normal, except for total blood protein, 5.0 gm/100 ml.; albumin, 3.0 gm/100 ml.; globulin, 2.0 gm/100 ml.; blood cholesterol, 600 mg/100 ml., and proteinuria, 8.5 gm/24 hours. P. S. P. excretion was 10% in 15 minutes, and the urea clearance was 48% of standard clearance. The urinary sediment revealed fatty casts and oval fat bodies. An intravenous pyelogram was normal, as was an ECG. A liver biopsy showed portal cirrhosis.

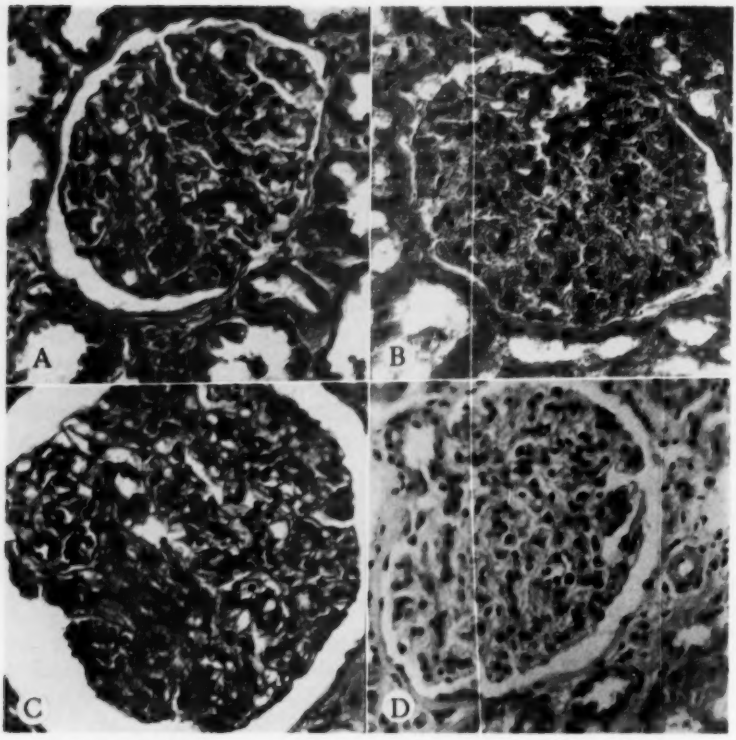

Fig. 2.—Pathology seen in chronic membranous glomerulonephritis.

Renal functions studied with inulin and PAH (Table 2) showed a diminished GFR and ERPF, with normal Tm_{PAH}; the calculated values of filtration fraction ($FF[C_{In}/C_{PAH}]$), GFR/Tm_{PAH}, and $ERPF/Tm_{PAH}$ were low, suggesting a glomerular lesion with normal tubules and without narrowing of the glomerular vessels. This was borne out on renal biopsy (Fig. 2*A*), which showed thickening of the glomerular basement membrane, with focal proliferative changes of the tuft. There was some thickening of the walls of the renal arterioles. The impression was that this represented chronic membranous glomerulonephritis.

He was discharged after one month, at which time he was asymptomatic, having lost the edema. His urine was clear and showed only a trace of albumin.

Case 7.—A 46-year-old man was admitted with a history of having "cat fever" while in service, nine years before admission. One year later he developed ascites and ankle edema. This persisted intermittently to the time of admission.

Examination showed blood pressure of 140/82 mm. Hg and pulse, 116. There was moderate cardiomegaly and hepatomegaly, but no edema. Initial laboratory tests, including blood cell count, blood urea nitrogen, total blood protein, blood cholesterol, and ECG, were normal. On urinalysis a specific gravity of 1.008, protein, and microscopically doubly refractile lipoid material were found. The urea clearance was 72% of maximum clearance, and P. S. P. excretion was 20% in 15 minutes. Twenty-four-hour urinary protein was 2.8 gm. per 100 ml. A diabetic glucose tolerance curve was found. Retrograde pyelography revealed a minimal left hydronephrosis. A renal biopsy was performed and findings were interpreted as showing chronic membranous glomerulonephritis (Fig. 2*B*) and demonstrated thickening of the basement membrane with focal proliferation in the glomerular tufts. The arterioles showed moderate thickening of the walls. There was some focal infiltration of lymphocytes.

On bed rest alone he lost 20 lb. in weight and was discharged after one month, edema-free.

Case 8.—A 36-year-old white man gave a history dating back two years before admission, beginning with a "cold" followed by dyspnea and night sweats. He was admitted to another Veterans' Administration Hospital, where he was thought to have pericarditis and hypertension. His hospital stay was accompanied by bouts of mild edema,

proteinuria, and polyuria. He was readmitted one year later, at which time he had hypertension (B. P. 160/130 mm. Hg) and minimal proteinuria. Three months later he again entered the hospital, with marked edema and proteinuria, and he was thought to have heart disease of an unknown type. Two years from his first hospital admission he was admitted to the Veterans' Administration Hospital in Washington, D. C., with a recurrence of edema.

At this time his blood pressure was 130/100 mm. Hg. His eyegrounds showed only arteriovenous nicking. Cardiomegaly, hepatomegaly, and leg edema were present.

Laboratory tests initially were normal (including blood cell count, total blood protein, serum cholesterol, and liver function tests), except for blood urea nitrogen of 26 mg/100 ml. and urinalysis showing proteinuria, numerous granular casts, a P. S. P. excretion of 10% in 15 minutes, and a urea clearance of 56% of standard clearance. A renal biopsy was consistent with a diagnosis of chronic membranous glomerulonephritis (Fig. 2*C*) and showed moderate thickening of the glomerular basement membrane with some narrowing of the capillary loops. In some glomeruli there was focal proliferation of cells. Coarse vacuoles were present in the cells of the proximal convoluted tubules, and the arterioles showed some thickening of the walls. On a low-sodium diet he lost the edema and was again discharged.

CASE 9.—A 55-year-old white male guard was first admitted to the hospital because of neurodermatitis. During his hospitalization proteinuria was found, and total serum protein was 5.2 gm/100 ml., with 3.4 gm. of albumin and 1.8 gm. of globulin per 100 ml. One year later he returned, with chills and fever beginning six weeks before admission. He responded well to therapy for pneumonia but continued to have a persistent cough.

Examination revealed only emphysema. His blood pressure, pulse, and temperature were normal.

Laboratory studies were normal, including a blood cell count, total protein, blood urea nitrogen, and ECG. On urinalysis proteinuria was found, with 4.0 gm/24 hours. P. S. P. excretion was 15% in 15 minutes. Renal biopsy was consistent with membranous glomerulonephritis (Fig. 1*D*). This showed diffuse thickening of the basement membrane in all glomeruli uniformly. The tubules were intact, and the arterioles were normal.

He responded to further antibiotic therapy and was discharged still having proteinuria.

Comment.—These four patients represent the same renal pathology occurring in the presence of symptoms most usually interpreted as heart disease, but with proteinuria and with fat in the urinary sediment. Their pertinent findings are shown in Table 3.

They differed from the five with the more acute illness in that their edema was less (three out of four), their proteinuria was less (0.6-8.5 gm/24 hours), and their urinary sediment was less striking, with fewer doubly refractile lipid bodies and Sudan-III-staining material, none of which was present in casts. Specific renal functions in one of these (Case 6) showed impaired filtration as the predominant abnormality. This patient also had an elevated blood pressure, but without the high FF (C_{In}/C_{PAH}) usually seen.

There was little difference between the two groups as far as P. S. P. excretion and urea clearance, although the latter was somewhat lower in the acute patients than in the chronic (39% as compared to 59%). In these patients, histories would indicate that their disease had been present for two to eight years prior to biopsy. This suggests that if a patient improves from his initial attack he probably has a good prognosis as far as life is concerned. Since the histology in the patients with "chronic" lesions differed very little from that seen in the second or third biopsy specimen from the patients with recovering "acute" lesions, these persons possibly remain static as far as their renal lesion is concerned for a considerable length of time, with periodic exacerbations of edema and proteinuria.

Cortisone therapy was followed by a decrease in proteinuria, edema and a rise in serum protein in three patients. It did not help in two patients, and four lost their edema without it, which suggests that those who responded may have done so anyway. Further work needs to be undertaken to correlate the steroid and corticotropin (ACTH) response reported[8-12] with the pathology present.

Comment

Allen[2] has reviewed the subject of membranous glomerulonephritis extensively. It is a lesion seen accompanying a number of

diseases, including typhus, malaria, eclampsia, and the reaction to cortisone, nitrogen mustards, and trimethadione (Tridione). It may, however, occur as a primary disease presenting as a nephrotic syndrome, with edema, proteinuria, hypoproteinemia, and hypercholesterolemia. Ellis [3] first suggested on clinical grounds that this picture might be a variant of acute glomerulonephritis (Type II nephritis) and differentiated it from the usual picture of acute glomerulonephritis (Type I nephritis). He felt that the prognosis of this syndrome was much poorer than in Type I nephritis. Postmortem examination in his patients months to years later demonstrated lobular glomerular lesions. These were seen in two of our patients (Cases 1 and 4), who progressed from the acute lesion to one of lobular glomerulonephritis.

Both Bell [1] and Allen [2] feel that the syndrome is a variant of acute glomerulonephritis, and Bell describes kidneys showing pathological changes of acute glomerulonephritis as well as membranous glomerulonephritis. Certainly in one of our cases (Case 3) lesions were found which appeared to be pathologically acute glomerulonephritis and then became characteristic of membranous glomerulonephritis. In one of our cases (Case 5) acute glomerulonephritis occurred in another member of the family just prior to the onset of membranous glomerulonephritis in the patient, again suggesting a relation between these two.

The lesion is a fairly common cause for the nephrotic syndrome, occurred in 9 of 28 patients with the syndrome, and was the second commonest cause for nephrosis, chronic glomerulonephritis being the commonest (Table 4).

Although the acute lesion seems to be a variant of acute glomerulonephritis, it differs in that a preceding history of infection is either ill-defined or absent.

It cannot be conclusively differentiated from the other causes of the nephrotic syndrome on clinical grounds alone. In those patients with a recurrence, edema may be the only symptom, while in the severer recurrence or in the patient with the acute lesion symptoms of uremia with nausea and vomiting may be present. Massive proteinuria is present, as is hypoproteinemia with an increase in α_2-globulin, hypercholesterolemia, and doubly refractile lipid bodies or Sudan-III-staining material in the urine sediment.

TABLE 4.—*Biopsy Diagnosis in the Nephrotic Syndrome*

	Cases
Chronic glomerulonephritis	10
Subacute glomerulonephritis	1
Membranous glomerulonephritis	9
Diabetic glomerulosclerosis	2
Arteriolar nephrosclerosis	5
Amyloidosis	1
	28

It differs from other forms of acute glomerulonephritis where proliferative changes are seen in the glomeruli in that the lesion consisting of thickening of the basement membrane persists or progresses rather than clearing in most instances.[13] This may serve as the pathological basis for the recurrences seen in the chronic form of the disease.

The final diagnosis of membranous glomerulonephritis depends on an adequate renal biopsy, but the disease should be suspected in any patient presenting for the first time with nephrosis.

Summary

Nine cases of membranous glomerulonephritis diagnosed by renal biopsy are presented. In one of the nine there was a histological evidence of a shift of the lesion from acute proliferative glomerulonephritis to membranous glomerulonephritis.

The lesion should be suspected whenever a patient presents with the nephrotic syndrome without a previous history of renal disease or with a history of similar episodes in the past with remissions, especially when renal function remains good.

Veterans' Administration Hospital, 2650 Wisconsin Ave., N. W. (7).

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Pericarditis Associated with Infectious Mononucleosis

LT. GERALD I. SHUGOLL (MC), U.S.N.

It is not surprising that the pericardium is involved in infectious mononucleosis, a disease of such protean manifestations. It is surprising that such a small number of cases of pericarditis associated with infectious mononucleosis have been reported. To date only 11 cases are in the literature. Pericarditis has been reported in association with other conditions, such as primary atypical pneumonia,[1] upper respiratory infections,[2] epidemic myositis,[3] lymphogranuloma venereum,[4] sinusitis,[5] and pharyngitis.[6]

It is the purpose of this report to present a case of pericarditis associated with infectious mononucleosis and to review the cases previously reported.

Report of a Case

A 22-year-old white man was admitted to the hospital on Oct. 21, 1956, with the chief complaint of severe crushing substernal pain of 10 hours' duration. He had been in good health previously, except for a mild nonproductive cough of 1 week's duration and a substernal soreness, aggravated by motion of the trunk, which had been present 15 hours previously. Ten hours prior to admission, while climbing stairs, he was suddenly seized with a severe pressing and constricting substernal pain ("like a straight-jacket"), followed by shortness of breath, palpitations, and sweating. The pain was constant and radiated to the neck and ears and was aggravated by movement of the trunk and deep breathing. The pain began to subside immediately upon admission to the hospital and initiation of bed rest.

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From the Cardiology Service, Department of Medicine, United States Naval Hospital, Bethesda, Md.

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Physical examination on admission revealed a well-developed well-nourished white man in no acute distress. Oral temperature was 100.4 F. The pulse was 100 and regular. Blood pressure was 130/84. The nasal mucous membranes were moderately hyperemic. The pharynx was normal. The neck veins were not distended or pulsating. The lungs were clear to percussion and auscultation. Auscultation of the heart revealed no rub, murmurs, or gallop. There was no enlargement of the liver or spleen. There was no significant lymphadenopathy.

Laboratory studies on admission revealed a white blood cell count of 9750, with 90% neutrophils, 8% lymphocytes, and 2% monocytes. The hemoglobin was 15.8 gm. per 100 cc.; hematocrit, 53%, and sedimentation rate (Cutler method), 15 mm. in one hour. Urinalysis, Kahn test, BUN, and cold agglutinins were normal. Skin tests with tuberculin intermediate, histoplasmin, and coccidioidin were negative. A throat culture eventually grew out Pseudomonas and Neisseria. The serum glutamic oxaloacetic transaminase was normal five days after admission. The C-reactive protein was negative, and the antistreptolysin titer was 125 units. Stool examination revealed no parasites.

X-ray of the chest revealed clear lung fields and a normal-sized heart. The electrocardiogram on admission was within normal limits.

The patient was kept at bed rest and received no specific treatment. The pain did not recur. A pericardial friction rub was never heard, despite daily auscultation. One day after admission the electrocardiogram showed marked ST-segment elevation in Leads II, III, aV_F, V_5, and V_6 (Fig. 1). Subsequent serial tracings showed ST- and T_2 wave changes consistent with pericarditis. The heart size as seen on x-ray did not change. Three days after admission the white blood cell count was 5300, with 28% neutrophils, 58% lymphocytes, 12% monocytes, and 2% eosinophils. Many atypical lymphocytes were noted. Two days later the Davidson heterophil agglutination titer was 1:56 presumptive and 1:14 after guinea-pig-kidney absorption. At this point, five days after admission, the patient complained of a sore throat. His pharynx was injected, and lymphoid hyperplasia became evident. Anterior cervical and axillary

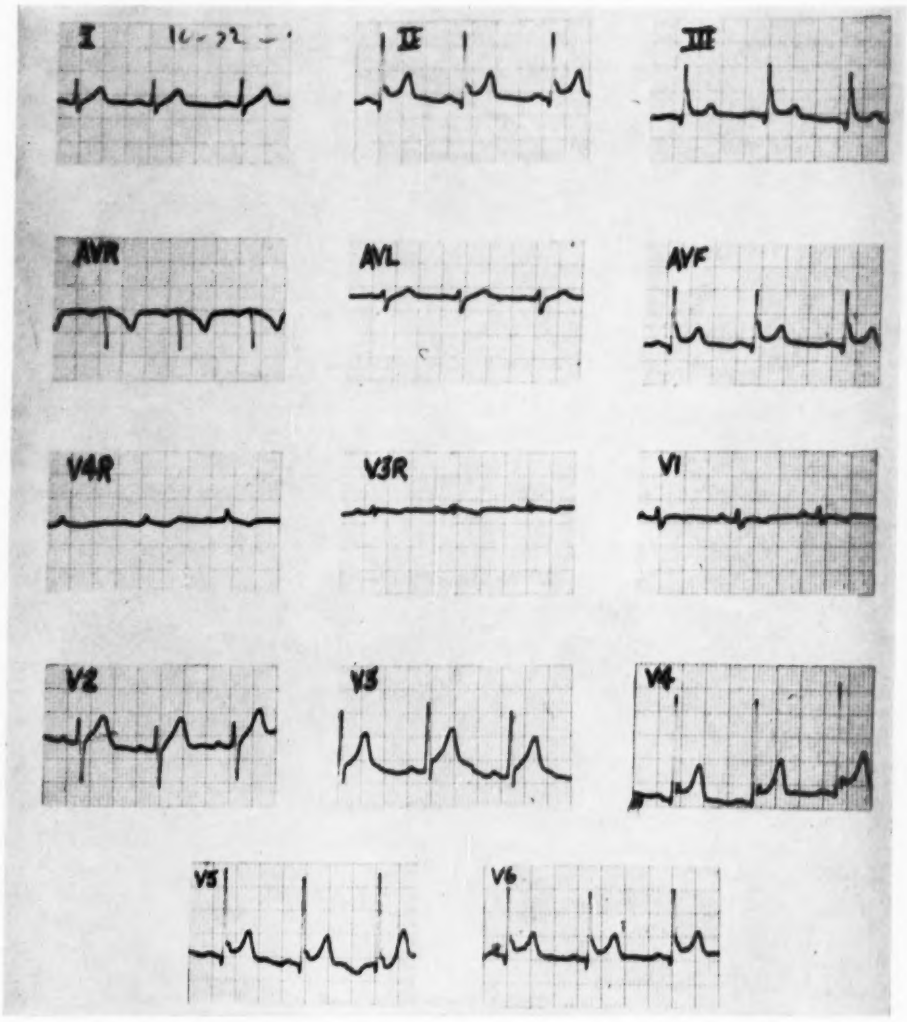

Fig. 1.—The electrocardiogram on the second hospital day, showing significant ST-segment elevation in Leads II, III, aV_F, V_4, V_5, and V_6. Note that there are no reciprocal depressions of ST segments in Leads I, aV_L, and medial precordial leads.

lymphadenopathy developed. Rectal temperatures, which had ranged from 100 to 100.6 F for the first three days, fell to normal. The heterophil titer rose to a peak of 1:448 (presumptive) and 1:224 (differential) by 10 days after admission. Repeat blood cell counts showed persistent relative lymphocytosis and many atypical lymphocytes until three weeks after admission. The sedimentation rate remained normal, and the C-reactive protein, negative. With no specific treatment the patient quickly became asymptomatic. The electrocardiograms continued to change until Dec. 11, 1956, when only slight ST-segment elevation remained, which could be considered within normal limits (Fig. 2) On Dec. 6 a pilonidal cyst, which had become infected Nov. 7, was excised without incident.

Comment

It is of interest that this patient presented with the features of acute pericarditis and then several days later developed the clinical, hematologic, and serologic characteristics of

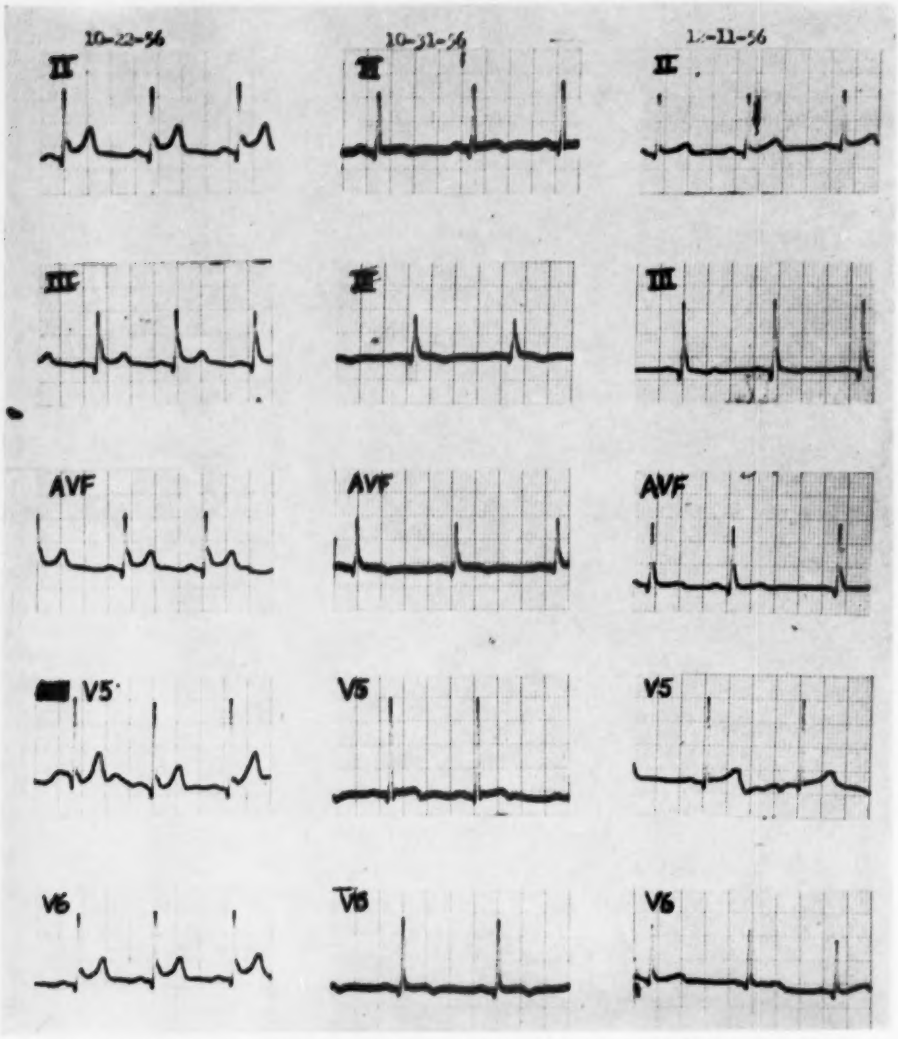

Fig. 2.—Significant serial changes in selected leads. Note return of ST segments almost to the isoelectric line and the T-wave inversions before the return to normal. Leads I and aV_L, not shown here, remained exactly as in Figure 1.

infectious mononucleosis. The diagnosis of pericarditis seems certain on clinical and electrocardiographic grounds.

Surprisingly few cases of pericarditis associated with infectious mononucleosis have been reported. Cardiac complications have, in general, been subclinical and benign and have been discovered during routine electrocardiographic examination. The abnormalities have consisted of nonspecific T-wave changes, disturbances in auriculoventricular conduction, premature beats, minor arrhythmias, and slight depression of ST segments.[7-9] Custer and Smith reported evidence at autopsy of myocarditis.[10]

Evans and Graybiel [11] reported four cases in which the electrocardiographic changes consisted primarily of slight inversion of, or low voltage of, the T waves. They felt that the T-wave changes persisted over a

longer period of time than would be expected if the myocardium alone was affected. Only one of the four presented with symptoms of pericardial involvement. One other had a pericardial friction rub. Otherwise pericarditis was diagnosed on the basis of incidental electrocardiograms. A fifth case presented as acute pericarditis with massive effusion, and the only positive findings in the work-up were an elevated heterophil agglutination titer and a lymphocytosis.

De Fazio and Marsico [12] reported a single case of infectious mononucleosis who manifested pain in the left scapular region, aggravated by breathing and coughing and gradually moving around to the precordium. The patient had a pericardial friction rub, cardiac enlargement on x-ray, and electrocardiographic changes consistent with acute pericarditis.

Miller et al.[13] reported three cases, two of whom presented with chest pains aggravated by cough or deep inspiration. Each had a friction rub and electrocardiographic changes consistent with pericarditis. Two of the three had reversible cardiac enlargement on x-ray.

Soloff and Zatuchni [14] reported a single case presenting with chest pains necessitating morphine for relief. No friction rub was mentioned, but the electrocardiogram was said to show ST-T changes consistent with pericarditis. Transient upper nodal rhythm was also noted.

Célice et al.[15] reported a case of a 23-year-old man who after eight days of palpitation presented with severe anterior chest pain. Serial electrocardiograms showed ST- and T-wave changes consistent with pericarditis. Infectious mononucleosis was apparent on clinical and hematologic grounds. No friction rub was noted. X-ray revealed no cardiac enlargement.

Twelve cases, including the one herein presented, of pericarditis associated with infectious mononucleosis have now been reported, ranging in age from 17 to 42. A friction rub was present in six. X-ray evidence of transient cardiac enlargement was present in four. One had a massive pericardial effusion. Eight presented with chest pain characteristic of acute pericarditis. All had electrocardiographic changes consistent with pericarditis, although a few of them showed only serial T-wave changes. All had a benign outcome.

Although it is possible that the occurrence of pericarditis with infectious mononucleosis is merely coincidental, it seems more likely that there is a true cause-and-effect relationship. Almost all major organs have been involved by this disease process, and microscopic evidence of myocardial involvement has been demonstrated. It seems logical, then, that the pericardium may be included. This suggests the possibility that the so-called acute benign idiopathic pericarditis is a clinical syndrome resulting from a variety of etiologic agents, of which infectious mononucleosis is only one.

Summary

A case of infectious mononucleosis that presented with the classical clinical and electrocardiographic features of acute pericarditis is described. The literature is reviewed, showing 11 previous cases. The suggestion is made that infectious mononucleosis may be just one of many causes of so-called acute benign idiopathic pericarditis.

Capt. R. J. Pearson Jr. (MC), USN, Chief, Cardiology Service, U. S. Naval Hospital, Bethesda, Md., gave counsel and assistance.

Cardiology Department, U. S. Naval Hospital, National Naval Medical Center, Bethesda 14, Md.

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The Significance of Alterations in Serum Enzymes in the Differential Diagnosis of Jaundice

FELIX WRÓBLEWSKI, M.D., New York

Introduction

The differential diagnosis in a patient presenting with jaundice rests primarily on a comprehensive historical review and a complete physical examination. Accordingly, in most instances, the type and cause of jaundice can be defined with resort to tests of urine, stool, and blood primarily to confirm the clinical impression. Occasionally the clinical setting makes the etiological explanation of jaundice obscure, and in these situations blood tests of liver function may contribute fundamentally to the diagnosis. The battery of liver function tests include measurements of a multiplicity of parameters of liver physiology, normal and pathologic. The contribution of each test may at times be crucial, but as a rule one test tends to confirm another and/or the clinical conclusion. With the increasing number of tests available to study liver disease clinically, a point of diminishing returns is reached if routine reliance is placed on a large battery of blood tests in evaluating the usual jaundice patient.

It is the purpose of this report to review the experience in the differential diagnosis of jaundiced patients at Memorial Center for Cancer and Allied Diseases, with an eye to defining the significance of alterations in serum enzymes in the differential diagnosis of jaundice. It is not the purpose of this presentation to detract from the contribution of any test of liver function and/or disease but rather to attempt to appraise the applicability of employing a limited number of blood enzyme determinations to confirm and/or establish the cause of hyperbilirubinemia in a given patient.

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Sloan-Kettering Institute and the Department of Medicine, Memorial Center for Cancer and Allied Diseases.

Methods and Materials

Patients were those seen on the wards and private services of Memorial Hospital and James Ewing Hospital. In all instances the patient presented with jaundice or when first seen had a bilirubin value of 2.0 mg. per 100 cc. or greater. All patients were reviewed anamnestically, were examined completely, and were studied by means of tests, including urinary bile and urobilinogen and the appearance of the stool. Serum total bilirubin and usually both direct and indirect bilirubin were determined. Serum alkaline phosphatase (method of Bodansky) and serum glutamic oxalacetic (SGO) and serum glutamic pyruvic (SGP) transaminases were measured.[1-4] In all instances, serum bilirubin, alkaline phosphatase, and transaminases were determined serially at varying intervals of four days or less. In addition, four or more of the following determinations were done in all patients: cephalin flocculation, thymol turbidity, total protein and albumin-globulin ratio, total cholesterol and cholesterol esters, prothrombin time, and sulfobromophthalein (Bromsulphalein) retention. The final clinical diagnosis was based on clinical course of the patient, operative findings, liver aspiration biopsy and/or autopsy finding. No patient was included in whom jaundice was adjudged to have resulted from two or more disease states. All laboratory determinations except serum transaminase tests were done in the clinical biochemistry laboratory of Memorial Center; SGO and SGP transaminase determinations were performed spectrophotometrically in the research laboratory at Sloan-Kettering Institute.[5,6] The normal range of values include serum bilirubin, 1.0 mg. per 100 cc. or less; serum alkaline phosphatase, 4.0 units or less; serum glutamic oxalacetic (SGO) transaminase, 40 units or less; serum glutamic pyruvic (SGP) transaminase, 35 units or less.

Results

Extrahepatic biliary obstructive jaundice is associated with increased serum alkaline

TABLE 1.—*Extrahepatic Biliary Tract Obstructive Jaundice*

Cause	Total Serum Bilirubin, Mg./100 Cc. (Range, 2.0-23.2)	Serum Alkaline Phosphatase, Units (Range, 8.0-45.0)	SGO Transaminase, Units (Range, 44-288)		SGP Transaminase, Units (Range 64-400)
Calculi	2.0- 8.0	10.0-22.2	44-187	<	88-300
Lymphomatous and leukemic nodes	3.5-18.0	8.0-38.0	44-288	<	64-400
Pancreatic cancer	4.0-17.9	28.0-40.0	112-120	<	168-216
Biliary tract cancer	16.0-23.2	17.5-49.1	112-140	<	136-180
Others	2.4-17.6	12.0-45.0	51-144	<	120-235

phosphatase of 10.0 to 45.0 units. Common-duct obstruction due to stones had values of 10.0 to 20.0 units, whereas that due to pancreatic tumor, pancreatitis, bile-duct carcinoma, and lymphomatous and leukemic nodes showed elevations of 12.0 to 45.0 units. Hyperbilirubinemia associated with common-duct obstruction due to calculi was from 2.0 to 8.0 mg. per 100 cc., whereas that associated with the other causes of extrahepatic biliary obstruction ranged from 2.4 to 17.9 mg. per 100 cc. In all instances the serum transaminase values were elevated and the SGP transaminase was greater than SGO transaminase activity. Calculous biliary obstruction was associated with SGP transaminase activity of 88 to 300 units and SGO transaminase values of 44 to 187 units. Obstruction due to other causes showed SGP transaminase activities which ranged from 99 to 400 and SGO transaminase values from 48 to 144 units. Table 1 summarizes the observations in regard to bilirubinemia and serum enzymes associated with extrahepatic biliary tract obstruction.

Intrahepatic carcinoma or lymphoma associated with hyperbilirubinemia is accompanied by elevations in serum alkaline phosphatase from 8.0 to 61.6 units. In some instances the increased serum alkaline phosphatase presumably reflects osteoblastic lesions as well as hepatic metastases. The total serum bilirubin varied from 2.3 to 12.2 mg. per 100 cc. In all cases of jaundice due to intrahepatic malignant disease serum transaminase values were above normal, and in all but one instance the SGO transaminase alteration was greater than the SGP transaminase. SGO transaminase varied from 43 to 300 units, while the SGP transaminase ranged from 26 to 240 units. One patient who had undergone a resection for pancreatic carcinoma reappeared with jaundice due to metastatic disease to the liver; total serum bilirubin was 12.2 mg. per 100 cc.; serum alkaline phosphatase, 14.3 units; SGO transaminase, 43 units, and SGP transaminase 46 units. Table 2 summarizes the observations in regard to bilirubinemia and serum enzymes associated with intrahepatic primary or metastatic carcinoma or lymphoma.

Laennec cirrhosis, when accompanied by hyperbilirubinemia of 2.0 to 9.5 mg. per 100 cc., is associated with serum alkaline phosphatase values which range from 4.0 to 10.4 units. In all patients studied SGO transaminase was abnormal and greater than SGP transaminase activity. SGO transaminase varied from 45 to 300 units, while

TABLE 2.—*Intrahepatic Primary and Metastatic Carcinoma and Lymphomas Associated with Jaundice*

Cause	Total Serum Bilirubin, Mg./100 Cc. (Range, 2.3-12.2)	Serum Alkaline Phosphatase, Units (Range, 8.0-61.6)	SGO Transaminase, Units (Range, 43-300)		SGP Transaminase, Units (Range 26-240)
Primary hepatoma	3.5- 5.2	8.3-12.0	100-180	>	64-90
Metastatic carcinoma	2.6-12.2	8.0-22.0	43-300	>	26-240
Lymphomatous involvement	2.3-10.0	3.8-61.6	128-160	>	22-133

TABLE 3.—*Cirrhosis Associated with Jaundice*

	Total Serum Bilirubin, Mg./100 Cc.	Serum Alkaline Phosphatase, Units	SGO Transaminase, Units	SGP Transaminase, Units
Laennec	2.4–9.5	4.0–10.4	45–300	> 20–258
Postnecrotic	7.8–8.0	10.0–15.2	140–200	> 50–120

SGP transaminase ranged from 20 to 258 units. In two patients with postnecrotic cirrhosis the bilirubinemia was 7.8 and 8.0 mg. per 100 cc., while the serum alkaline phosphatase was 10.0 and 15.2 units, respectively. The SGO transaminase was elevated to 140 and 200 units and the SGP transaminase to 50 and 120 units, respectively. Table 3 summarizes the observations in regard to bilirubinemia and serum enzymes associated with active Laennec and postnecrotic cirrhosis.

Acute homologous serum hepatitis, infectious hepatitis, and hepatitis associated with infectious mononucleosis during the initial or increasing icteric phase of the disease are associated with serum alkaline phosphatase values which range from 4.0 to 11.2 units during the period when the bilirubinemia varied from 2.0 to 30.4 mg. per 100 cc. Concomitantly, the SGO transaminase was increased from 460 to 2140, and the SGP transaminase, from 600 to 2600 units. No difference was observed between homologous serum and infectious hepatitis and the alterations of the serum enzymes. The natural history of acute hepatitis is one which includes an initial, or increasing, icteric phase and a convalescent, or decreasing, icteric phase. It is noteworthy to emphasize that the challenge in regard to the differential diagnosis of jaundice presents during the initial or increasing icteric phase and usually not during the convalescent phase. As the jaundice reaches a peak and begins to wane the serum transaminase activities as a rule fall rapidly toward normal. During both phases of acute hepatitis—initial, or increasing, icteric phase and subsequent, or decreasing, icteric phase—the bilirubinemia ranged from 2.0 to 30.4 mg. per 100 cc.; the serum alkaline phosphatase, from 4.0 to 11.2 units; the SGO transaminase, from 40 to 2140, and SGP transaminase, from 60 to 2600 units. During the initial increasing icteric phase the SGO transaminase is above 500 and the SGP transaminase, above 600, while in the decreasing icteric phase the transaminase activities fall below these levels. One can determine in which phase the patient is by assessing the serial changes in the hyperbilirubinemia in relation to the level of the transaminases.

Hepatotoxic drugs produce hepatitis by a variety of pathophysiologic mechanisms, and on the type of hepatic injury will depend the alterations in the serum enzymes. Carbon tetrachloride was found usually to increase SGP transaminase greater than SGO transaminase, and the levels attained depended on the estimated amount and duration of toxic exposure. In all instances the alkaline phosphatase did not increase above 5.0 units. Chlorpromazine hyperbilirubinemia of 2.0 to 7.0 mg. per 100 cc. was associated with increments of serum alkaline phosphate from 9.6 to 11.4 units. The SGP transaminase was greater than the SGO transaminase activity, ranging from 68 to 72 units in the latter and 176 to 300 units in the former. Other drugs, such as Azaserine (O-diazoacetyl-L-serine) mercaptopurine, bishydroxycoumarin (Dicumarol), salicylates, and pyrazinamide, when hepatotoxic result in increased SGP transaminase greater than SGO transaminase with varying increases in serum alkaline phosphatase. Observations during toxic hepatitis included hyperbilirubinemia from 2.0 to 9.0 mg. per 100 cc., serum alkaline phosphatase from 2.0 to 11.0 units, SGO transaminase from 35 to 4100 units, and SGP transaminase from 120 to 4200 units. In all cases, with discontinuance of exposure to the hepatotoxic agent the serum transaminase activities began to decrease toward normal.

TABLE 4.—*Acute Homologous Serum and Infectious Hepatitis Associated with Jaundice*

	Total Serum Bilirubin, Mg./100 Cc.	Serum Alkaline Phosphatase, Units	SGO Transaminase, Units		SGP Transaminase, Units
Initial or increasing icteric phase	2.0–30.4	4.0–11.2	460–2,140	<	600–2,600
Convalescent or decreasing icteric phase	2.0–30.4	4.0–11.2	40–2,140	<	60–2,600

Hemolytic jaundice in the adult was noted to increase serum total bilirubinemia from 2.4 to 6.6 mg. per 100 cc., while the serum alkaline phosphatase varied from 3.0 to 4.3 units. Little or no elevation above the normal range (20 to 40 units) was noted for SGP transaminase, while the SGO transaminase varied from 32 to 140 units. In most instances of hemolytic jaundice, both serum transaminase and serum alkaline phosphatase remained within normal limits of activity.

Comment

Although a battery of liver function blood tests may at times be necessary to help define the etiologic explanation of hyperbilirubinemia in the jaundiced patient, in most instances the laboratory information will suffice if limited to the determination of the serum total bilirubin, serum alkaline phosphatase, and serum transaminase. Table 5 summarizes the alterations in these serum enzymes as seen in most patients presenting with icterus. Extrahepatic biliary obstructive jaundice is readily differentiated from that due to acute homologous serum and infectious hepatitis by the fact that the serum alkaline phosphatase is usually higher in the former than the latter. As a rule in the initial or increasing icteric phase of acute hepatitis both serum transaminase values are well over 400 units, while in obstructive jaundice the serum transaminase values are usually below 400. In both instances, SGP transaminase is greater than the simultaneously measured SGO transaminase activity. In addition, the serial alterations in the serum enzymes in obstructive jaundice and jaundice associated with acute hepatitis are readily distinguishable. Figures 1 and 2 depict the alterations in serum total bilirubin and serum enzymes in a patient with acute extrahepatic obstructive jaundice and in a patient with acute hepatitis. The serum enzyme alterations are quantitatively and serially distinct in the two types of jaundice. Although toxic hepatitis due to drugs may mimic the serum enzyme alterations seen in obstructive jaundice, especially as in the case of chlorpromazine when the alkaline phosphatase may become appreciably elevated, hepatitis due to hepatoxic agents may be readily distinguished from obstructive jaundice and acute hepatitis. When the toxic insult to the liver is stopped by the discontinuance of the administration of hepatoxic agent, the serum transaminases begin to fall at once toward normal even though the serum bilirubin and/or serum

TABLE 5.—*Comparison of Ranges of Serum Enzyme Activities in Patients with Various Types of Jaundice*

Cause	Serum Alkaline Phosphatase, Units	SGO Transaminase, Units		SGP Transaminase, Units
Extrahepatic biliary tract obstruction	8.0–45.0	44–288	<	64–400
Intrahepatic primary and metastatic carcinoma or lymphoma	8.0–61.6	43–300	>	26–240
Acute homologous serum and infectious hepatitis (increasing icteric phase)	4.0–11.2	460–2,140	<	600–2,600
Cirrhosis	4.0–15.2	45–300	>	20–258
Hepatotoxic drugs *	3.5–11.4	68–370	>	176–440
Hemolysis	3.0– 4.3	32–140	>	20–40

* Excluding carbon tetrachloride.

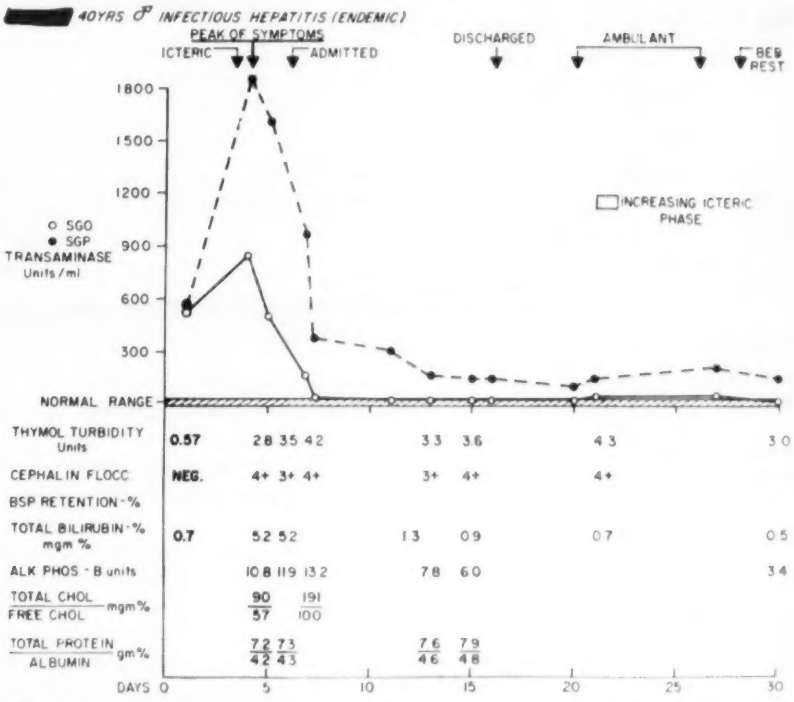

Fig. 1.—Alterations of serum enzyme activities and tests of liver function in the case of a patient with acute infectious hepatitis.

alkaline phosphatase may transiently remain unchanged or even increase.

Intrahepatic carcinoma and lymphoma associated with jaundice present serum enzyme changes similar to those observed in cases of cirrhosis. However, in most instances of active Laennec cirrhosis with hyperbilirubinemia the serum alkaline phosphatase is normal or only slightly elevated, while in most cases of intrahepatic malignant neoplasm with jaundice the alkaline phosphatase is appreciably elevated above normal. Postnecrotic cirrhosis, unlike Laennec's, may be associated with an elevated serum alkaline phosphatase activity and consequently may present serum enzyme alterations which mimic those observed in intrahepatic neoplasia with jaundice. Hemolytic jaundice in the adult is usually readily distinguishable from other causes of jaundice; in most instances the serum enzymes remain normal except for transient and slight elevations in SGO transaminase, with little or no alteration of SGP transaminase above the normal range.

Most types of surgically amendable jaundice, extrahepatic biliary tract obstructive jaundice, can be distinguished laboratory-wise from medical types of jaundice by the characteristic alterations in serum enzymes. In obstructive jaundice, serum alkaline phosphatase is elevated usually to a level greater than 10 units. SGP transaminase is increased to a greater extent than the simultaneously measured SGO transaminase, the former usually to levels less than 400 and the latter, less than 300 units. In all the types of medical jaundice other than acute hepatitis SGO transaminase values are greater than simultaneously determined SGP transaminase activity. In the case of acute hepatitis in the increasing icteric phase, when SGP transaminase is greater than SGO transaminase the values of the serum transaminases are greater than 600 and 500 units, respectively.

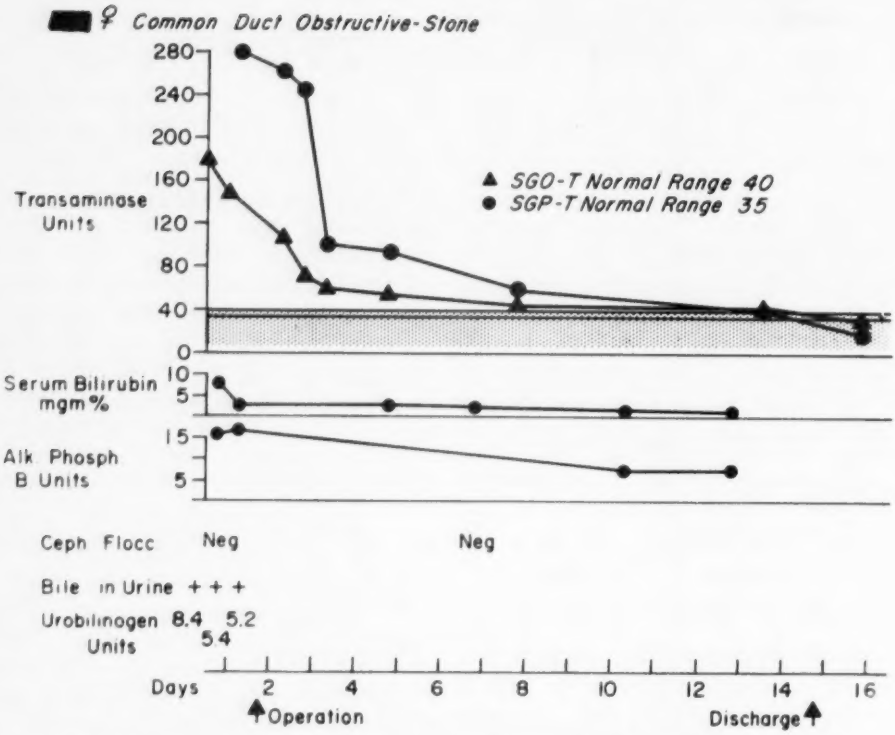

Fig. 2.—Alterations of serum enzyme activities and tests of liver function in the case of a patient with calculous biliary tract obstruction.

When acute hepatitis is superimposed on a liver containing metastatic deposits, the SGO transaminase may be greater than the SGP transaminase. This turn of events has been found to be associated with an abnormal serum protein electrophoretic pattern, including elevated β- and γ-globulins. However, in spite of the greater SGO transaminase than SGP transaminase, the values of the serum transaminases are usually greater than 600 in the initial, or increasing, icteric phase of the hepatitis. When obstructive jaundice occurs in a patient with metastatic liver disease, SGP transaminase may be greater than, equal to, or somewhat less than the SGO transaminase activity. However, the serum transaminase values rarely go above 300 units even at bilirubinemias of 30 mg. per 100 cc. or more.

Certain icteric patients present in a clinical setting which challenges the clinician even when armed with all the diagnostic armamentaria, let alone the information derived from serum enzyme studies. Suffice it to say the court of final appeal in all instances involving the differential diagnosis of jaundice is the clinician himself, who must intelligently synthesize the diagnostic conclusion from all the facts, history, physical examination, laboratory tests, clinical course, surgical exploration, and therapeutic response. There is no implication intended that a complete battery of liver function tests at times may not contribute crucial or pivotal information. It is suggested, however, that in clinical instances of patients presenting with jaundice, alterations in serum transaminase (SGO transaminase and SGP transaminase) along with changes in serum alkaline phosphatase and serum bilirubin may prove useful in resolving the etiological explanation for icterus.

Summary

The experience in the differential diagnosis of jaundiced patients at Memorial Center is reviewed with an eye to defining the significance of alterations in serum enzymes in the differential diagnosis of jaundice.

Alterations in serum alkaline phosphatase, serum glutamic oxalacetic (SGO) transaminase, and serum glutamic pyruvic (SGP) transaminase activities were correlated with the total serum bilirubin and the clinical conclusion.

When the history and physical examination are supplemented by information of the activity of serum alkaline phosphatase and SGO and SGP transaminases, the differential diagnosis of most icteric patients can be resolved.

Most types of surgically amendable jaundice, extrahepatic biliary tract obstructive jaundice, can be distinguished laboratory-wise from medical types by the characteristic alterations in serum enzymes.

Obstructive jaundice is usually associated with a serum alkaline phosphatase of greater than 10 units. SGP transaminase is increased to a greater extent than the simultaneously increased SGO transaminase, the former usually to levels less than 400 and the latter, less than 300 units.

In most types of medical jaundice other than acute hepatitis, SGO transaminase values are greater than the simultaneously determined SGP transaminase activity. In the case of acute hepatitis in the increasing icteric phase, when SGP transaminase is greater than SGO transaminase, the values of the serum transaminases are greater than 600 and 500 units, respectively.

It is suggested that in clinical instances of patients presenting with jaundice alterations in serum transaminase along with changes in serum alkaline phosphatase and serum bilirubin may prove useful in resolving the etiological explanation for icterus.

Memorial Center for Cancer and Allied Diseases, 444 E. 68th St. (21).

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Chronic Treatment of Toxic Diffuse Goiter

WILLIAM S. REVENO, M.D., and HERBERT ROSENBAUM, M.D., Detroit

As widely accepted as are surgery and radioiodine in the treatment of toxic diffuse goiter there still remains a group of patients in which results are not satisfactory or the therapy is not applicable. Among these are the patients with postoperative recurrence or progressive exophthalmos, children for whom neither form of treatment yields consistently good results,[1,2] those under 40 and those with some form of chemical block for whom I^{131} is either contraindicated or thwarted and surgery is unacceptable, and those who qualify for either form of treatment but refuse to accept it. Treatment of this group with the antithyroid drugs alone has achieved desired results in no more than 50% to 60%; for while thyroxin formation is blocked by these agents, the stimulus from the anterior pituitary remains. Thus relapse may follow when treatment is discontinued, and thyroid hyperplasia continues undiminished.

The suppressive action of desiccated thyroid on the normal thyroid by way of the anterior pituitary offers the means for enhancing the effectiveness of the antithyroid drugs.[3-10] By its addition when the hyperthyroidism has been controlled, the continuing pituitary stimulus may be curbed and the uncertain and undesirable side-effects of the antithyroids eliminated.

Impressed by this potentiality, we have during the past eight years treated 21 patients by first administering an antithyroid drug and then adding desiccated thyroid in increments of 15 mg. daily when euthyroidism has been well established. This combination when tolerated was continued for a varying period, the desiccated thyroid being gradually increased and the antithyroid reduced and finally eliminated. The former agent was then given alone and continued for an indefinite period.

In this group of 21 patients (Table) ranging in age from 12 to 58 years there were 18 females and 3 males. Five had recurrence after thyroidectomy, and two were girls aged 12 and 14 years; eight had a severe form of the disease, three had a complicating exophthalmos, and 3 had a relatively mild form of the disease.

Recurrent Disease

All of the five patients responded promptly to treatment. Four (1, 2, 4, 5) had been given antithyroids for prolonged periods before addition of desiccated thyroid was tried. They had been euthyroid while under this regimen but relapsed on discontinuing treatment. When desiccated thyroid was added it was soon possible to reduce then discontinue the antithyroids without interrupting the remission. One patient (Patient 3) who had had two thyroidectomies had been given combined treatment for 22 months when both drugs were stopped, and the remission has continued for over 4 years. The other patients have been taking from 15 to 180 mg. of desiccated thyroid for four to seven years. The abbreviated history of one of these patients follows.

This 45-year-old white woman (Patient 5) was first seen in 1946 because of severe hyperthyroidism recurrent six years after thyroidectomy. A second operation had been refused. Remission occurred after two months' treatment with propylthiouracil, which was then continued for a total of 51 months. Several attempts at discontinuing the antithyroid were followed by a return of symptoms. Dessicated thyroid, 15 mg. at first then 30 mg. daily, was added and the combination continued for four months. The antithyroid was then discontinued, and the patient has remained euthyroid on treat-

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From the Department of Medicine, Harper Hospital, and Wayne State University College of Medicine.

Data on Twenty-One Patients

Patient	Age	Sex	Antithyroid Alone, Mo.	Combined Therapy, Mo.	Desiccated Thyroid Alone, Mo.	Length of Remission, Mo.	Result
				Recurrent Disease			
1	38	F	17	13	44	70	Euthyroid
2	40	M	66	7	15	68	Euthyroid
3	33	F	1.5	22	..	52	Euthyroid
4	40	F	29	7	37	85	Euthyroid
5	45	F	51	4	48	48	Euthyroid
				Children			
6	12	F	6	17	5	30	Euthyroid
7	14	F	4	5	11	60	Euthyroid
				Complicating Exophthalmos			
8	49	F	3	13	12	12	Euthyroid and exophthalmos improved
9	58	F	40	7	..	?	Controlled
10	44	F	3	18	..	?	Controlled
				Severe Hyperthyroidism			
11	19	M	34	16	27	27	Euthyroid
12	43	F	9	3	2	48	Euthyroid
13	27	F	2.5	1	8.5	24	Euthyroid
14	52	F	4	29	3	51	Euthyroid
15	29	F	4	8	9	9	Euthyroid ?
16	29	M	8	16	..	..	Euthyroid ?
17	26	F	4	5	..	..	Euthyroid ?
18	34	F	4	24	9	..	Relapse
				Mild Hyperthyroidism			
19	34	F	2	3	38	38	Euthyroid
20	31	F	13	..	8	8	Euthyroid
21	22	F	3	2	48	48	Euthyroid

ment with 30 mg. desiccated thyroid for the past four years.

Hyperthyroidism in Children

The 12- and 14-year-old girls with the primary disease (Patients 6 and 7) responded to the treatment in satisfactory manner, and both continued in remission after desiccated thyroid was discontinued. The younger patient was followed for only 2½ years, but the other one, having reached remission after 4 months of antithyroids, continued in that state during 5 months of combined therapy then 11 months on therapy with 60 mg. desiccated thyroid alone. She has remained euthyroid during the past five years without any treatment.

Complicating Exophthalmos

None of the three patients (Patients 8, 9, and 10) with this complication had a severe form of hyperthyroidism. Their thyroid glands were not markedly enlarged, and the B. M. R.'s were under +40%, but nervousness, tachycardia, and excessive perspiration were very marked. All had exophthalmos, but the disturbing part was that one eye protruded more than the other. As difficult as it is to predict whether exophthalmos will progress after suppression of the thyroid, this sign is foreboding to us, and we are loath to subject such patients to either surgery or radioiodine, preferring the more flexible method of treatment.

One of these patients (Patient 8), a woman aged 49 with symptoms of 1 year's duration, was maintained in the euthyroid state for 16 months on combined therapy. The exophthalmos receded gradually and has practically disappeared while the patient was taking 60 mg. of desiccated thyroid daily during the past year.

The second patient (Patient 9), a woman aged 58, had been treated with antithyroids intermittently for a year and when first seen by us showed bilateral diffuse goiter with bruit, a B. M. R. of +31%, a blood pressure of 200/90, and marked unilateral exophthalmos. She responded well to methimazole but could not tolerate the addition of desiccated thyroid. After seven months' trial the effort was abandoned, and the antithyroids alone have been continued for the past two years. Now, while the B. M. R. varies between +18% and −13% and the blood pressure remains elevated (190/90 to 170/90), the thyroid gland has become barely palpable and the exophthalmos has receded appreciably.

The third patient (Patient 10), a 44-year-old woman with toxic diffuse goiter of two years' duration, responded very well to antithyroids after three months, but the exophthalmos increased notably. Desiccated thyroid was added in increasing amounts up to 60 mg. daily during the next 3 months, and the combination has been continued for the past 15 months. The euthyroid state has been maintained, and the exophthalmos has receded slightly.

Severe Hyperthyroidism

Eight patients with severe toxic diffuse goiter elected chronic treatment rather than surgical or radioiodine therapy. Two were males aged 19 and 29 years, and 6 were females ranging in age from 26 to 52. The oldest female (Patient 14) had been given strong iodine (Lugol's) solution for 12 years and became euthyroid after 4 months of antithyroid therapy. This was combined with desiccated thyroid for 29 months, then the latter was continued alone for 3 months. She has now been euthyroid for 51 months without treatment.

The next oldest patient (Patient 12), with symptoms of 15 months' duration, was treated with methimazole alone for 9 months, then desiccated thyroid was added for 3 months, and the latter was continued alone for 2 more months. The established euthyroid state has continued without interruption for the last 50 months.

The other six patients, two of whom were males, had much in common. All had very severe classic hyperthyroidism, with high B. M. R.'s. They were markedly hyperkinetic and unstable, requiring continuous sedation, and were unacceptable for I^{131} therapy because of age.

One patient (Patient 13), a woman aged 27, became euthyroid after 10 weeks of antithyroids, remained so with combined therapy for 4 weeks, and continued in this state for the next 24 months while taking 30 mg. of desiccated thyroid alone. She has not been heard from since; so her present status is unknown.

A second patient (Patient 1), a youth aged 19 when first seen, was maintained on antithyroids alone for 34 months, then on combined therapy for 16 months, and on 60 mg. of desiccated thyroid alone for the next 27 months. There was still slight thyroid enlargement and some exophthalmos at this time, and the patient insisted on radioiodine treatment. He received 6 mc. of I^{131} and within six weeks developed severe myxedema that now requires 180 mg. of desiccated thyroid daily for control.

The remaining four patients responded satisfactorily to the antithyroids in from four to eight months and maintained the euthyroid state on combined therapy, but in two (Patients 16 and 17) several attempts to discontinue the antithyroids were followed by recurrence of the hyperthyroidism, so combined therapy is being continued. The other two patients were transferred to treatment with desiccated thyroid alone and tolerated it well at first. However, one of these (Patient 18), with marked emotional instability, relapsed after nine months and has been restarted on the antithyroids. The other (Patient 15) is continuing with desiccated thyroid alone, and while the markedly enlarged thyroid and exophthalmos have receded steadily and she is essentially euthyroid, her status is uncertain because of an unstable personality.

Mild Hyperthyroidism

The three patients with mild hyperthyroidism (Patients 19, 20, and 21) achieved and maintained remission promptly and without significant difficulty.

The first, a 34-year-old woman with symptoms of 6 months' duration, became euthyroid after 2 months of antithyroids, was maintained on combined therapy for 3 months, and has remained euthyroid on 60 mg. desiccated thyroid for the past 38 months.

The second patient, aged 31, with symptoms of three months' duration, became pregnant shortly after treatment was started with propylthiouracil. Although well con-

trolled, she developed leukopenia, and so methimazole was substituted. Leukopenia reappeared, but the methimazole was continued in smaller dosage, and she was carried uneventfully through the seventh month, when strong iodine solution was substituted. Normal delivery occurred at term. Five months later symptoms recurred, and when methimazole was given leukopenia followed. Potassium perchlorate was substituted and continued for six months, at which time it was replaced by a daily dose of 15 mg. desiccated thyroid. This has been continued for the past eight months, and the patient has remained euthyroid. This patient is again pregnant (sixth month) and remains euthyroid while taking 30 mg. of desiccated thyroid daily.

The third patient, a woman aged 22 with hyperthyroidism for 15 months, responded well to methimazole after 11 weeks, was then given combined therapy for 8 weeks, and has remained euthyroid on therapy with 120 mg. of desiccated thyroid daily for the past 4 years. During this time she has had a normal pregnancy without return of the hyperthyroidism.

Summary

In review, 15 of the 21 patients have been euthyroid for from eight months to seven years following chronic treatment. Nine of these are still taking from 15 to 180 mg. of desiccated thyroid daily, while six require no medication.

Five of the successfully controlled group had had recurrence following previous thyroidectomy; two were children, one had questionable progressive exophthalmos, four had a severe form, and three had a mild form of toxic diffuse goiter.

Of the remaining six patients, one with progressive exophthalmos could not tolerate desiccated thyroid, but both the hyperthyroidism and the exophthalmos have been controlled with antithyroids alone. A second patient with a similar disturbance is also controlled but with combined therapy.

In four patients with severe hyperthyroidism the desired result has not yet been achieved: two continuing on combined therapy; one controlled, but precariously, with desiccated thyroid alone, and one restarted on antithyroid therapy after relapse. The patients in this group impress us, because their disease was interlaced with varying degrees of psychogenic disorder, as similar to those in whom complications are most likely to follow other methods of treatment.

While some of these six patients may still be salvaged their treatments must for the present be counted as failures.

The success in 70% of the patients treated by the method described, while better than that achieved with the antithyroids alone, remains below the 80% to 90% successes reported for surgery and I^{131} therapy. Exact comparisons are difficult because of the small number studied. Treatment here took longer, but most of these patients presented a special problem, and some, at least, might have fared no better had they been treated otherwise.

Conclusions

It would seem from the experience reported here that the door need not be closed to those who (1) reject present-day treatment, whether for recurrent or for primary toxic diffuse goiter, or (2) are under 40 and generally considered unacceptable for I^{131} therapy. In the case of children where there is valid difference of opinion regarding use of a destructive procedure, a trial of the method described here certainly carries small risk, as it does also in patients with mild toxic diffuse goiter.

In any of these situations this flexible treatment procedure does not exclude either surgery or I^{131} therapy at any time.

968 Fisher Bldg. (2).

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Case Reports

Combined Congenital Subaortic Stenosis and Infundibular Subpulmonic Stenosis

Report of a Case with Successful Surgical Treatment

EARL F. BEARD, M.D.; DENTON A. COOLEY, M.D., and JOSEPH R. LATSON, M.D., Houston, Texas

Congenital subaortic stenosis and infundibular or subvalvular pulmonic stenosis are relatively common congenital cardiac anomalies when they occur singly as isolated defects or in association with other intracardiac deformities. Recently a case with both aortic and pulmonic subvalvular stenoses was studied in which no other associated lesions were present, and the diagnosis was made before operation by cardiac catheterization. We are unaware of any previously reported cases of a similar nature. Surgical correction of both lesions was successful, utilizing temporary cardiopulmonary bypass.

Report of Case

A 19-year-old white youth was admitted to St. Luke's Episcopal Hospital on Dec. 10, 1956, for cardiac studies. A cardiac murmur was first noted during an attack of pneumonia during infancy. He developed more slowly than normal and was considerably smaller than his siblings; at age 12 years he weighed 68 lb. Typical anginal pains on exertion appeared during his high school years, and since that time his exercise tolerance has gradually decreased until the present, when angina occurred on climbing one flight of stairs or attempting to walk rapidly or run. He had experienced no syncope, convulsions, dyspnea, edema, or cyanosis. Ten siblings were all living and in good health.

Physical examination revealed a moderately well-developed person who was 66 in. tall and weighed 114 lb. Blood pressure in the right arm was 90/66 mm. Hg. The precordium was somewhat prominent, and the cardiac apex impulse was in the midaxillary line. A strong systolic thrill was palpable over the upper sternal region. A very loud harsh systolic murmur was audible in the same location but loudest in the right second and third interspaces and was transmitted over the entire precordium and into the carotid, subclavian, and brachial arteries. In fact, the murmur was audible over the upper sternum with the stethoscope held 1 cm. away from the skin. Both aortic and pulmonic second sounds were present, though diminished in intensity. Lungs were clear to auscultation, and there were no signs of congestive cardiac failure.

Routine laboratory studies were within normal limits. Roentgenograms and fluoroscopy of the chest revealed cardiac enlargement, predominantly left ventricular (Fig. 1). Electrocardiograms were indicative of left ventricular hypertrophy without evidence of hypertrophy of the right ventricle (Fig. 2).

On Dec. 12, 1957, right heart catheterization was performed, with the results shown in Table 1. Withdrawal of the catheter from the main pulmonary artery to the mid right ventricle revealed a typical infundibular chamber with an intermediate pressure (Fig. 3). Findings at catheterization eliminated the possibility of an intracardiac shunt. Pressure recorded in the femoral artery was 100/64 mm. Hg, with a tracing indicating moderate anacrotic notching.

Thoracotomy was performed Dec. 14, 1956, with use of a bilateral anterior transverse incision entering the right third and left fourth intercostal spaces. A typical infundibular chamber measuring about 3 cm. in diameter was evident in the outflow tract of the right ventricle, and a harsh systolic thrill was palpable in the pulmonary artery. A much harsher thrill was palpable in the ascending aorta, but neither aorta nor pulmonary artery

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From the Cardiac Clinic, St. Luke's Episcopal and Texas Children's Hospitals.

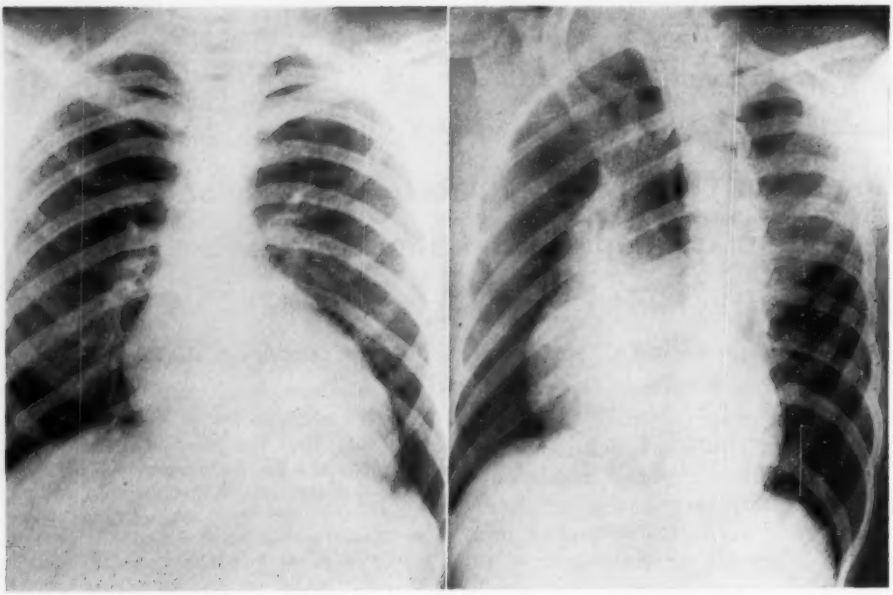

Fig. 1.—Roentgenograms of the chest in posteroanterior and left anterio-oblique positions, showing evidence of marked left ventricular hypertrophy.

Fig. 2.—Electrocardiogram made before operation, showing standard bipolar and unipolar extremity leads with representative right and left precordial unipolar leads. The tracing was interpreted as being indicative of left ventricular hypertrophy without evidence of right ventricular hypertrophy.

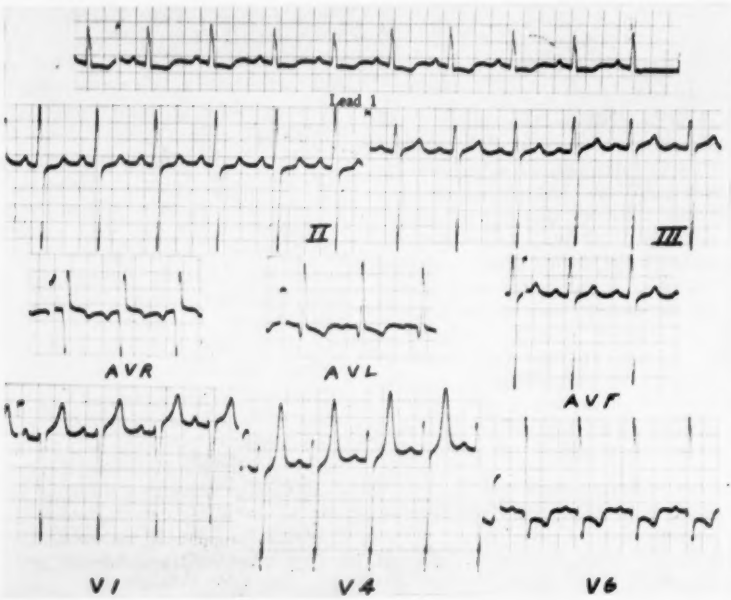

TABLE 1.—*Findings on Right Heart Catheterization*

Location of Catheter	Pressure, (Mm. Hg)	Oxygen Saturation, %
Right pulmonary artery	15/10	75
Main pulmonary artery	15/10	74
Infundibular chamber	40/10	73
Right ventricle (mid)	100/2	72
Right atrium (low)	8/2	70
Right atrium (mid)	8/2	70
Superior vena cava	8/2	68
Femoral artery	115/60	99

were dilated or otherwise unusual. The left ventricle made up the major bulk of the enlarged heart. Preparations were made for temporary cardiopulmonary bypass by cannulating the superior and inferior vena cavae for the outflow of venous blood and the left femoral artery for return of oxygenated blood after a method previously described.[1] A pump oxygenator system modified after the DeWall-Lillehei device[2] was used, and a flow rate of 35 cc. or 1820 cc. per kilogram body weight per minute was employed. Shortly after total body perfusion was started the ascending aorta was occluded, and cardiac arrest was produced by injecting 70 cc. of 2.5% solution potassium citrate slowly into the proximal aortic segment until cessation of cardiac activity resulted.

After cardiac arrest was produced a right ventriculotomy incision was made, with extension of the incision through the fibromuscular infundibular ridge. The stenosis was approximately 1.5 cm. in diameter. With use of a special adenoid punch the obstructing ridge was resected, following which the right ventriculotomy was repaired with a continuous nonabsorbable (silk) surgical suture. Then the ascending aorta was incised, and the aortic valves were exposed. The leaflets were normal, but about 1 cm. beneath them was a subvalvular fibrous membrane with an eccentrically placed orifice barely admitting a finger tip. This membrane was excised with scissors, and the outflow tract of the left ventricle was dilated thoroughly with an exploring dilator. The aortotomy incision was repaired with continuous nonabsorbable surgical sutures, and the distal clamp on the ascending aorta was released. As the potassium solution was flushed out of the coronary system, cardiac action resumed, and effective circulation was promptly restored. Duration of total cardiopulmonary bypass was 18 minutes and of cardiac arrest, 16 minutes.

Pressure recordings made at operation before and after repair of the defects were as shown in Table 2.

The patient's recovery from operation was uneventful, and he was discharged from the hospital on the 10th day after operation. A systolic murmur of softer intensity persisted over the base

Fig. 3.—Continuously recorded pressure tracing with simultaneous electrocardiogram made at cardiac catheterization during withdrawal of the catheter from the main pulmonary artery to the right ventricle. The extremely low pressures at the left of the tracing (15/10 mm. Hg) were recorded in the main pulmonary artery; the intermediate pressures (40/10 mm. Hg) in the center were recorded in the infundibular chamber, and those at the right (100/2 mm. Hg) were recorded with the catheter tip in the mid right ventricle.

TABLE 2.—*Pressure Recordings Made at Operation Before and After Repair of Defects*

	Pressure, Mm. Hg	
	Before	After
Right ventricle (mid)	95/0	30/0
Right ventricle (infundibular)	32/0	20/0
Pulmonary artery	38/22	20/5
Left ventricle	165/0	128/4
Aorta	105/60	88/36

of the heart, but the thrill had disappeared. Blood pressure in the arms was 130/80 mm. Hg. Subsequent examination six weeks later revealed a basal diastolic murmur transmited down the left sternal border and a blood pressure of 130/60 mm. Hg. The findings were considered to be indicative of mild aortic regurgitation, in spite of the fact that the aortic leaflets were not damaged at operation. The patient was walking moderate distances without experiencing angina or dyspnea.

Summary

A case of congenital combined subaortic stenosis and infundibular pulmonic stenosis with intact cardiac septa is presented in which the symptoms and clinical findings of subaortic stenosis obscured completely the infundibular pulmonic stenosis. The presence of the infundibular lesion was discovered at cardiac catheterization. Both lesions were successfully corrected during temporary cardiopulmonary bypass, with use of a pump oxygenator.

Kelsey and Leary Clinic, 6655 Travis St. (25).

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Progressive Diffuse Interstitial Fibrosis of the Lungs (Hamman-Rich Syndrome)

Report of a Case of Seven Years' Duration

FERRALL H. MOORE, M.D.; JOHN W. HAMLIN, M.D., and STUART LINDSAY, M.D., Redwood City, Calif.

Since Hamman and Rich,[1] in 1944, first described the syndrome now bearing their names, a number of similar cases have been reported. The present report of an additional case seems warranted because of a known duration of seven years with clinical and radiological observations and because of an associated hyperglobulinemia and pathological cardiac, renal, and splenic lesions.

Report of Case

History.—A 42-year-old white housewife of French extraction was first seen in March, 1947, because of fatigue and amenorrhea of two months' duration. She gave a history of several common childhood diseases. There had been no operations or injuries. The family history was noncontributory. There was no history of exposure to industrial dusts or chemicals.

In 1927, the patient was hospitalized in a sanatorium. A diagnosis of pulmonary tuberculosis, Stage I, was made. The record did not disclose whether or not a positive sputum had been found or whether tuberculin testing had been done. Films of that date were not available for review. The patient was discharged after 11 months of bed rest. Since 1928, she had two spontaneous abortions. In 1938, she had a full-term normal pregnancy and a normal infant.

Physical examination revealed a middle-aged woman of moderate build, who was not acutely ill. Low-grade fever (temperature of 99-99.6 F) was present. No thyroid enlargement or adenopathy was noted. The breasts were normal on palpation. No evidence of cardiovascular disease was found.

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From the Medical Service and Laboratory of the Sequoia Hospital, Redwood City, Calif., and the Department of Pathology, University of California School of Medicine, San Francisco.

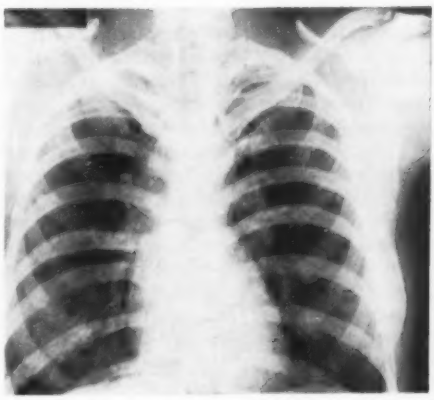


Fig. 1.—Roentgenogram of chest (March, 1947), showing localized fibrosis at the left apex.

The blood pressure was 120/70. Transient rales after coughing were heard beneath the right clavicle. Abdominal, pelvic, and neuromuscular examinations were negative. A roentgenogram of the chest (Fig. 1) revealed fibrosis at the left apex. A slightly positive skin reaction was present to PPD No. 1. No acid-fast bacilli were found in the sputum. The corrected sedimentation rate was 41 mm. in one hour. A moderate nonspecific anemia was noted. The red blood cell count was 3,350,000 per cubic millimeter, and the hemoglobin was 10.3 gm. per 100 cc. The leukocyte count and differential count were normal. Urinalysis gave normal findings.

After two months of bed rest, the patient had gained 5 lb. The sedimentation rate remained at 40 mm. in one hour. Serial chest films examined during the next three months showed no change of the pulmonary lesion. Repeated sputum examinations revealed no tubercle bacilli. Occult blood was not found in the stool while the patient was on a meat-free diet. Complete roentgenograms of the gastroenteric tract revealed no lesions. Iron given orally, liver extract given parenterally, and high vitamin intake had only slight effect on the anemia.

Course.—During 1948 and 1949 the patient carried on a modified rest program and refused care in the sanatorium despite the diagnosis of chronic fibroid tuberculosis. Relief from menopausal flushes and sweating resulted from administration of estrogen orally, and the patient felt improved, despite a continued elevation of the sedimentation rate. In March, 1950, an attack of acute pleural pain with fever occurred, and the patient consented to care in a sanatorium. During the next five months she remained at bed rest with streptomycin and aminosalicylic acid (PAS) therapy. During this period scattered densities, mottling, and fibrosis, visible in chest films, had appeared throughout the right lung and at the apex. Bronchoscopic examination revealed no abnormalities. The sputum and gastric washings remained free of tubercle bacilli.

A uterine curettage, performed in September, 1950, because of menorrhagia, yielded cystic hyperplastic endometrium. She returned home in October, 1950, for a further rest regimen. During 1951-52, the pulmonary lesion did not progress further, although on several occasions acute episodes of cough, fever, and malaise occurred and responded promptly to administration of penicillin or oxytetracycline (Terramycin). Recurrent pain in the right hip and sacroiliac joints was treated symptomatically. Roentgen examination revealed no skeletal lesions.

Her status remained unchanged, and she was moderately active until November, 1953, when recurrent substernal exertional pain associated with breathlessness, tachycardia, and dry cough appeared. Subcrepitant and crepitant rales were heard over the right chest both anteriorly and posteriorly and beneath the left clavicle. Moderate clubbing of the fingers and slight cyanosis of the lips and nail beds were manifest. An electrocardiogram showed no significant abnormalities. Response to administration of glyceryl trinitrate (nitroglycerin) was equivocal, and breathlessness and tachycardia were not influenced by digitalization. After four weeks at bed rest, exercise tolerance without substernal pain or breathlessness did not improve, and she entered the hospital.

A chest film (Fig. 2) revealed extensive interstitial pulmonary infiltration, interpreted as nontuberculous in origin and compatible with pulmonary adenomatosis or sarcoidosis. Examination of the iliac bone marrow revealed mild hypoplasia. Biopsy of a supraclavicular node showed normal lymphatic tissue. No sarcoid lesions were present. No acral changes were seen in x-ray films of the hands. The serum calcium was 9.7 mg. per 100 cc., and the total plasma protein level was 8.4 gm., with albumin 4.2 gm. per 100 cc. and globulin 4.2 gm. per 100 cc. The sputum remained negative for tubercle bacilli. The sedimentation rate varied from 39 to 45 mm. in one hour. Blood culture was negative.

The clinical course of the disease during the previous seven years had not been typical of tuberculosis but was more suggestive of a sarcoidosis or diffuse pulmonary fibrosis. There was no history of exposure to industrial dust or chemicals, and the duration of the disease seemed to rule out pulmonary adenomatosis. Because of the rapidly progressive course of the disease, steroid therapy seemed justified and was initiated in January, 1954. Hydrocortisone, 60 mg. orally, was administered daily. In addition, dihydrostreptomycin was administered intramuscularly during the first three months. For the next eight months the patient was more active and without dyspnea or angina. The red blood cell count and hemoglobin reached normal levels for the first time. Typical steroid euphoria with slight facial edema and hirsutism developed despite reduction in dosage of hydrocortisone to 40 mg. daily. Serial chest films examined at two- to four-week intervals showed no significant change in the appearance of the infiltrating pulmonary lesion. The sedimentation rate, however, remained above 40 mm. in one hour.

In June and August, 1954, recurrent acute febrile episodes, with increased cough, occurred and responded promptly to tetracycline. In July, 1954, left uveitis with associated corneal ulceration developed and reponded to local administration of cortisone ointment and sulfacetamide.

In September, 1954, the downhill course was more rapid and accompanied by progressively severer dyspnea on exertion. Increasingly frequent paroxysms of nonproductive cough and dyspnea required oxygen for relief. Clubbing of the nails became more pronounced. Variable crackling and subcrepitant rales were heard beneath the clavicles and at the bases. The expiratory phase of respira-

Fig. 2.—Roentgenogram of chest (January, 1953), showing diffuse bilateral interstitial pulmonary infiltration.

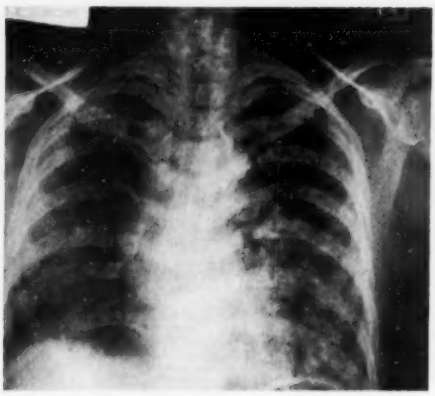


Fig. 3.—Roentgenogram of chest (September, 1954), showing more extensive diffuse fibronodular pulmonary infiltration.

tion became much prolonged, and the pulmonic and aortic second sounds were equalized. The serum albumin was 3.48 gm. per 100 cc., and the serum globulin, 3.57 gm. per 100 cc. A complete blood cell count was normal. Adequate digitalization did not affect a tachycardia of 110 to 120 per minute. At this time the dosage of hydrocortisone was increased again to 80 mg. daily. A chest film (Fig. 3) showed extensive and widely distributed fibronodular pulmonary lesions of greater extent than noted in chest films a few months previously.

Dosage of hydrocortisone was increased to 90 mg. daily, and slight remission in dyspnea and cough resulted. During the next few weeks there was a temporary decrease in pulmonary distress, but by November, 1954, frequent exacerbations of fever, cough, and dyspnea recurred. Daily administration of corticotropin intramuscularly for a brief period was of no distinct benefit. By early December, 1954, the patient required oxygen continuously. Daily administration of tetracycline was necessary to prevent prompt recurrence of acute pneumonitis. Clubbing of the fingers and prolongation of expiration became more pronounced. The patient died suddenly Dec. 13, 1954.

Autopsy Report.—Gross Examination: The autopsy revealed a well-developed and well-nourished woman. The skin and mucous membranes were normal, and there was no edema or peripheral external lymphadenopathy. Clubbing of the fingers and toes was noted. Pleural fibrosis with adhesions was noted, but the pericardial and abdominal cavities were normal. The heart weighed 390 gm. Hypertrophy of both ventricular walls was present, the right ventricle measuring 9 mm. in thickness, and the left ventricle, 14.0 mm. The myocardium was normal otherwise. An area of endocardial thickening was noted at the base of the tricuspid valve, associated with fibrous thickening of the cusps. The other valves appeared normal. The coronary arteries had thin elastic pliable walls and were not obstructed.

The pleural surfaces were mottled and varied from reddish-brown and purplish-blue. Frothy mucoid exudate was present in the bronchial tree. No evidences of obstruction or neoplasm of the bronchial system were noted. The hilar lymph nodes were small and pigmented. The pulmonary artery and its branches were free of abnormality. The lungs were heavy (1400 gm. each), uniformly firm, and fibrous. All lobes were very firm and had an unusual gritty character on section. The cut surfaces showed a mottled, pale gray and reddish-brown, fibrous appearance. Some of the smaller bronchi were moderately dilated.

The liver, gallbladder, and biliary tract were grossly normal. No unusual findings were noted in the pancreas, gastrointestinal tract, or mesenteric nodes. The adrenal glands showed significant thinning of the cortex, but the medullas were normal. No gross abnormality of the kidneys was present. The spleen was small and weighed 90 gm. The remainder of the tissues and organs, including the brain, were not significantly altered.

Microscopic Examination: Microscopic examination revealed abnormalities of the heart, lungs, spleen, and kidney. The myocardium showed slight hypertrophy of the myocardial fibers. Minimal atherosclerosis of the coronary vessels was present. None of the valves, save the tricuspid, were remarkable. The tricuspid valve, however, showed thickening. One cusp was fibrotic, and there was considerable separation of the connective tissue fibers and nuclei by fibrinary eosinophilic intercellular material. A small fibrinoid vegetation projected through the endothelium.

An extensive fibrosing process obliterated most of the pulmonary parenchyma (Fig. 4). The pleura was thickened and consisted of vascular dense collagenous connective tissue infiltrated with chronic inflammatory cells. Most bronchi were abnormal. Many showed hypertrophy and hyperplasia of the muscular layers associated with fibrous thickening and acute and chronic inflammatory infiltration of their walls. Extensive loss of bronchial elastic tissue was observed. In some bronchi the proliferating connective tissue elevated the mucosa. Little respiratory epithelium remained in the bronchi, being mostly replaced by a single layer of cuboidal epithelium or by metaplastic squamous cells. Almost all bronchial cartilage had disappeared.

Similar changes were observed in the bronchioles, although squamous metaplasia was more pronounced. Much of the parenchyma had been completely replaced by moderately dense, cellular, and vascular collagenous connective tissue containing focal collections of lymphocytes and plasma cells. Where alveoli remained, there was considerable

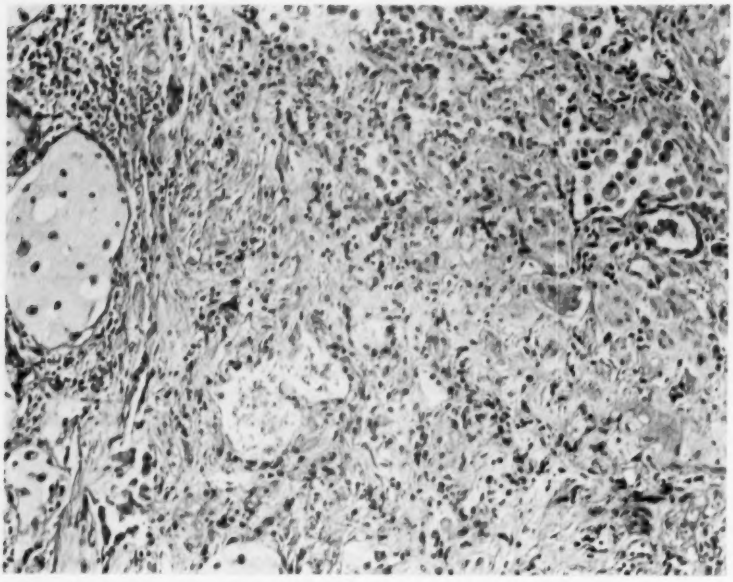
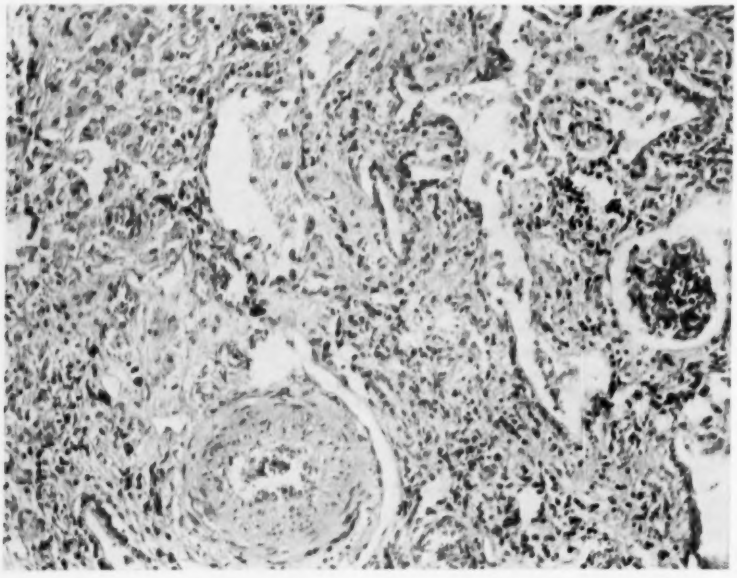


Fig. 4.—Pulmonary parenchyma, displaying pronounced interstitial and intra-alveolar fibrosis. Minimal chronic inflammation is present. Hematoxylin and eosin; × 250.

interstitial fibrosis and chronic inflammation widening alveolar walls and compressing alveolar spaces. Many alveoli were partially or completely filled with fibrinous exudate undergoing organization by connective tissue and endothelium. This intra-alveolar organization led to formation of structures resembling Masson bodies and eventually to complete alveolar obliteration. Some remaining alveoli

Fig. 5.—The residual alveoli are partially lined by cuboidal epithelium and contain fluid and mononuclear cells. The pulmonary arterial branch shows concentric fibrous intimal thickening. Hematoxylin and eosin; × 250.



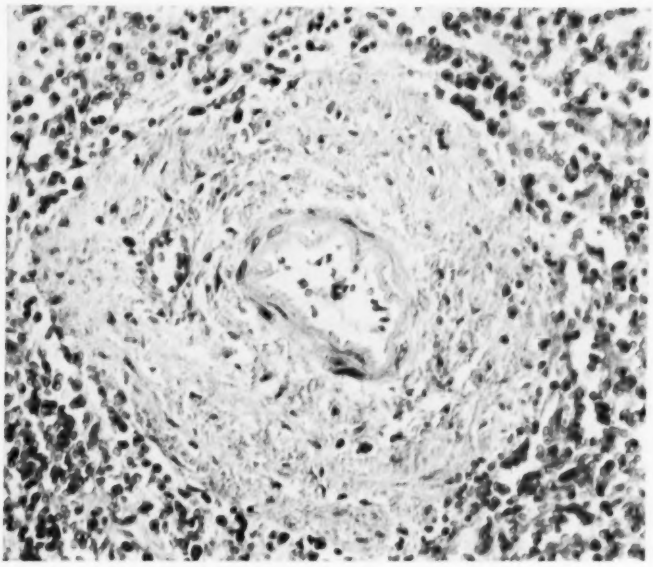


Fig. 6.—Splenic artery with periarterial fibrosis. Hematoxylin and eosin; × 500.

were dilated and lined either by a single layer of columnar ciliated epithelial cells, by pleomorphic cuboidular columnar epithelial cells, or, in some instances, by metaplastic squamous epithelium. As a rule, the remaining dilated alveoli were filled with mucoid fluid containing macrophages and leukocytes. Dense connective tissue obliterating alveoli contained coarse fragmented segments of elastic tissue, presumably derived from alveolar walls. Proliferating smooth-muscle cells observed throughout the fibrosing process were derived both from arterial media and from bronchial musculature. Examination of the pulmonary tissues with polarized light failed to demonstrate refractile material. Spectrographic analysis of pulmonary tissue showed no unusual chemicals to be present.

Many diseased pulmonary arterial branches were observed. Some displayed intimal fibrous thickening associated with medial muscular hypertrophy (Fig. 5). In others, the intimal thickening was eccentric and the intimal connective tissue infiltrated with acute and chronic inflammatory cells. Significant degrees of narrowing of the vascular lumens resulted from this process.

Pronounced congestion of the central portions of the hepatic lobules with atrophy of parenchymal cells was observed. The Kupffer cells were not remarkable, and the portal areas showed no fibrosis or inflammatory exudate.

The splenic capsule showed moderate focal fibrosis. Small lymphoid Malpighian follicles lacked germinal centers. The splenic pulp was congested and contained large numbers of plasma cells, lymphocytes, and histiocytes. The trabeculae were not abnormal. Periarterial fibrosis of some medium-sized arteries was observed (Fig. 6). Although pronounced, it did not have the distinct concentric laminations characteristic of lupus erythematosus. The arterioles were not altered.

The gastrointestinal tract and pancreas were not remarkable.

The kidneys showed minimal arteriosclerosis. A few peripheral hyalinized glomeruli were present, and in some glomeruli portions of the tufts had moderately thickened basement membranes resembling the wire-looping characteristic of lupus erythematosus. No hyalin thrombi or fibrinoid degeneration were observed in these glomeruli, and the capillary endothelium was normal. The renal tubules and pelvic tissues were not abnormal.

The adrenal glands had moderate cortical atrophy, but the lipid content was adequate, and the three cortical zones were well demarcated. The medullary tissue was not unusual.

The thyroid gland showed a normal histologic pattern. The sternal bone marrow showed normal proportionate distribution of cellular elements in normal amounts. Microscopic examinations of other tissues showed no significant abnormalities.

Comment

In 1944, Hamman and Rich [1] described three fatal cases of "acute diffuse interstitial fibrosis of the lung." The duration of the disease ranged from 31 days to 5 months, and the course was characterized by rapid progression of increasing dyspnea and cyanosis, with final cardiac failure. Autopsy

examination revealed extensive connective-tissue hyperplasia of the pulmonary interstitial structures. The alveoli contained little or no cellular inflammatory exudate, but their walls were tremendously thickened from fibroblastic proliferation progressing to dense fibrosis. The etiology was unknown.

Eder, Hawn, and Thorn,[2] in 1945, reported a similar case of four months' duration and emphasized the proliferation and prominence of lining alveolar cells in the lung. Potter and Gerber,[3] in 1948, published their observations on another such patient, who died after an illness of 32 weeks' duration. The disparity between the minimal auscultatory findings during life and the extensive pathologic lesions noted in chest films and at autopsy was explained by the essentially interstitial nature of the lesion. No inclusion bodies suggestive of a viral pneumonitis were found, and no chemical etiology was discovered in the patient's background. Ferrari et al.,[4] in 1949, first expanded the concept of acute pulmonary fibrosis and reported two cases of 5 and 12 months' duration, respectively, with similar clinical course and pathological findings. The emergence of subacute and chronic forms of the acute phase described by Hamman and Rich [1] was predicted. No etiologic factor was determined. Peabody et al.,[5] in 1950, first described this syndrome in identical twins. One died more than three years after the onset of the illness. The other survived but had clinical and radiologic evidence confirming the diagnosis. The fact that these identical twins had led widely separated lives for 25 years prior to the onset of the disease indicated an inherent constitutional tendency. These observers believed the disease to be a prolonged chronic process, remaining subclinical until depletion of respiratory reserve, when the rapidly progressive terminal phase appeared. Humphreys,[6] in 1951, commented on chronic progressive diffuse pulmonary disease of idiopathic type as distinguished from those forms due to berylliosis, sarcoidosis, or pneumoconiosis. The possible role played by diffuse connective tissue disease in the production of this condition was mentioned. Callahan et al.,[7] in 1952, reported on the use of corticotropin and cortisone in the treatment of a patient also having carcinoma of the bronchus. Questionable benefit resulted from this therapy. Golden and Bronk,[8] in 1953, cited three cases of this syndrome with autopsy findings. Examination of pulmonary tissues by phase microscopy and special staining methods revealed pronounced thickening of the alveolar septa due to capillary proliferation and reticulum and collagenous hyperplasia. It was emphasized that the pulmonary fibrosis in systemic scleroderma was collagenous rather than vascular. Peabody,[9] in 1953, reported an additional case and commented on suppression of the disease by cortisone or corticotropin and warned of the swiftly fatal termination which might follow reduction of maintenance dosage of the steroid. Reservation of these compounds for the seriously ill patient was advised. Rubin,[10] in 1955, cited four cases of diffuse interstitial pulmonary fibrosis in rheumatoid disease and commented on the similarity of the pathologic findings of the Hamman-Rich syndrome to those found in certain collagen diseases or hyperergic states and in cases of unresolved atypical pneumonias with organization. Wildberger and Barclay [11] contributed further to knowledge of this syndrome by reporting fatal cases of siblings, aged 52 and 38 years and living in widely separated parts of the country, and by describing the radiologic and pathologic findings. These observers noted the transient benefit obtained from steroid therapy and also commented on the rapid deterioration of the patient occurring with reduction of the established maintenance dosage. Guillaudeu and Jaquet [12] reported an additional case of interstitial pulmonary fibrosis in which hydrocortisone therapy was believed to have prolonged the course of the disease. These authors thought an altered state of tissue reactivity was present in this disease process.

In the case presented in this paper, certain features seem significant as etiologic of the nature of this disease. Hyperglobulinemia

paralleling that found in three cases of rheumatoid disease with diffuse interstitial pulmonary fibrosis reported by Rubin [10] and in one of the two patients with this syndrome reported by Wildberger [11] suggests the presence of a systemic condition with pulmonary manifestations rather than isolated pulmonary fibrosis. Multiple myeloma, sarcoidosis, and malignant neoplasm were ruled out by autopsy. A tricuspid valvular vegetation, thickened renal glomerular basement membranes, and splenic periarterial fibrosis were similar although not identical to the lesions found in disseminated lupus erythematosus, a collagen disorder. The absence of extrinsic etiologic factors disclosed either in the history, in the histologic pattern of the pulmonary lesion, or on examination of pulmonary tissue by polarized light or spectrographic analysis excludes a diagnosis of inhalant or chemical pneumoconiosis. The prolonged duration of seven years, greater than in other cases cited, may have permitted the gradual involvement of tissues other than the lungs, whatever the basic etiologic factor. The significant benefits produced initially by steroid therapy, which halted the clinical progress of the disease for many months, resembled those conferred by the steroids on certain others of the diffuse connective tissue or collagen diseases.

Conclusion

The association of progressive interstitial pulmonary fibrosis with hyperglobulinemia and evidences of generalized disease of connective tissues of the heart, spleen, and kidney but without the histologic features of pneumoconiosis, sarcoidosis, scleroderma, or the infectious granulomas may be more than coincidental. Further correlation of the clinical, laboratory, and pathologic findings in similar cases is urged to determine whether the syndrome of idiopathic progressive interstitial pulmonary fibrosis is a pathological entity or whether it is a local manifestation of a diffuse disease of connective tissue.

Redwood Medical Clinic, 2946 Broadway.

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Adrenocortical Carcinoma with Hyperadrenocorticism

A Clinical, Metabolic, and Hormonal Study

HERTA SPENCER, M.D.; ISAAC LEWIN, M.D.; DANIEL LASZLO, M.D., New York; ROY HERTZ, M.D., Bethesda, Md.; ATTALLAH KAPPAS, M.D., and THOMAS F. GALLAGHER, Ph.D., New York

The cooperative effort of three groups of investigators made it possible to study the clinical course and the metabolic and hormonal derangement of a patient with adrenal carcinoma and the responsiveness of the tumor to hormone stimulation and Amphenone (1,2-bis[*p*-aminophenyl]-2-methylpropanone-1-dihydrochloride) therapy.[1-5] This study covers a period of four years during which three stages of the course of Cushing's syndrome were investigated. The first stage illustrates the presence of significant hormonal and metabolic aberrations, although there was a paucity of clinical signs and symptoms. The second stage, which followed the removal of an adrenal tumor, illustrates the reversibility of Cushing's syndrome in both clinical and biochemical parameters. This remission, considered to be a "cure," lasted, however, only approximately three and one-half years. It was interrupted by the sudden emergence of pronounced virilization associated with significant hormonal and metabolic aberrations. This third stage was due to widespread metastases of a hormone-producing adrenal cortical carcinoma. It was possible to demonstrate at this time that this highly malignant tumor was responsive to hormonal and chemotherapeutic influence. Hormone production of this tumor was unequivocally increased by adrenocorticotropin, probably depressed by exogenous cortisone, and significantly inhibited by Amphenone.[6-8]

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I. Clinical Course

STAGE 1.—*Early Cushing's Syndrome Due to an Adrenal "Adenoma"*

A 42-year-old woman was admitted to Montefiore Hospital in November, 1951, with a tentative diagnosis of Cushing's syndrome because of hypertension and slight hirsutism present for many years, sudden development of amenorrhea, and "fullness of the face." There was a history of familial hypertrichosis. She had shaved her face and legs since puberty, and the hair growth on the abdomen had increased recently. Menses were normal until the onset of amenorrhea, four months prior to hospitalization. Symptoms of pregnancy or menopause were denied. Aches in the legs and tiredness present for many years were pronounced for eight months and were related to emotional difficulties. She had "migraine" headaches in the past, and recently, occasional frontal headaches. The weight remained constant (115 lb. [52.2 kg.]) for the past five years. There was no history of easy bruisability, back pain, change in libido, edema, polydipsia or polyuria, heat intolerance, or infection. She had not received any hormone therapy.

The patient was of normal female contour; weight was 52.3 kg.; height, 160 cm. There was no acne, striae, ecchymosis, moon facies, or abnormal fat distribution. Fine hair growth was present on the face and coarse hair on the forearms and thighs. Some hair extended from the mons pubis toward the umbilicus, but there was no distinct male escutcheon. There was no bone tenderness or kyphosis. The thyroid gland was not enlarged. The blood pressure was 170/105 mm. Hg. There was minimal hypertensive retinopathy, and the cardiac status was within normal limits. No abdominal organs or masses were palpable. On pelvic examination a uterine mass, assumed to be a fibromyoma, was felt, and the clitoris seemed to be slightly enlarged.

The frog test for pregnancy was negative, and there was no evidence of pheochromocytoma. The

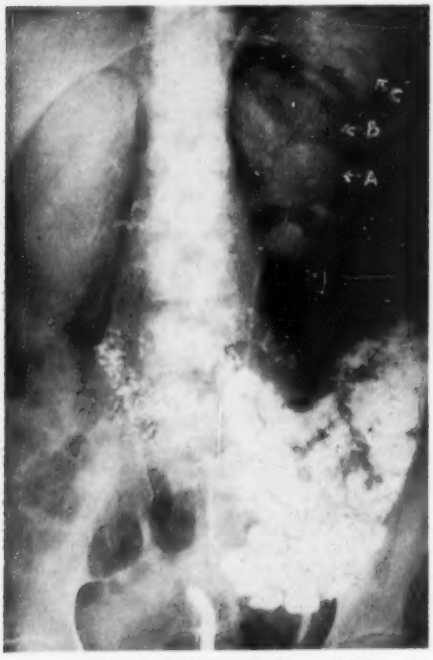

Fig. 1.—Presacral air insufflation and left retrograde pyelogram. A large suprarenal mass is present. *A*, upper pole of left kidney. *B*, suprarenal mass. *C*, spleen.

visual fields were normal. The roentgenograms of the skull were normal; those of the spine showed minimal osteoporosis. The intravenous pyelogram showed the left kidney to be lower than the right. Therefore, a presacral air insufflation was performed which showed a left suprarenal mass (Fig. 1).

The results of the various laboratory tests are listed in Table 1. The oral glucose tolerance test was diabetic in type (Fig. 2, Curve *A*). The serum calcium was determined five times and ranged from 11.1 to 11.9 mg. per 100 cc., except on one occasion, when it was 13.2 mg. per 100 cc.

After completion of the clinical, metabolic, and hormone studies, the patient received 40 mg. of corticotropin (ACTH) on two days prior to operation, and cortisone was added on the day of operation.

A left translumbar exploration* revealed replacement of almost the entire left adrenal by a well-encapsulated yellowish friable tumor measuring 10×9×9 cm. and weighing 140 gm. (Fig. 3). Histologically it was an adrenocortical tumor (Fig. 4), showing focal areas of bizarre cells and increased mitotic activity.

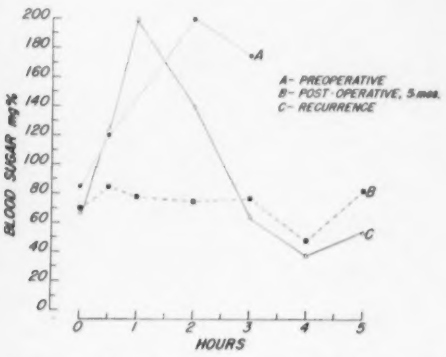

Fig. 2.—Oral glucose tolerance test performed in the three stages of the disease.

STAGE 2.—*Recovery from Cushing's Syndrome and Development of Hypoadrenalism*

The patient had hypotension, elevation of temperature, anorexia, and lassitude on the first postoperative day. Three such episodes recurred later, concomitant with the discontinuation of hormone therapy. These symptoms disappeared promptly after corticotropin therapy was reinstituted. This indicated the responsiveness of the remaining right adrenal gland to corticotropin.

The hypertrichosis of the face started to clear within six weeks following the operation and disappeared four months later. Menses reappeared two and one-half months after removal of the adrenal "adenoma." The patient continued to complain of fatigue for several months after the operation, but she resumed work eventually. She received occasional small doses of corticotropin or cortisone, with variable relief of symptoms. Hypoadrenalism was suspected. The serum electrolytes,

Fig. 3.—Gross specimen of left adrenal tumor, measuring 10×9×9 cm., weight, 140 gm. (surgical specimen).

* Operation was performed by Dr. L. A. Orkin, Attending Surgeon in Urology, Montefiore Hospital, on Dec. 19, 1951.

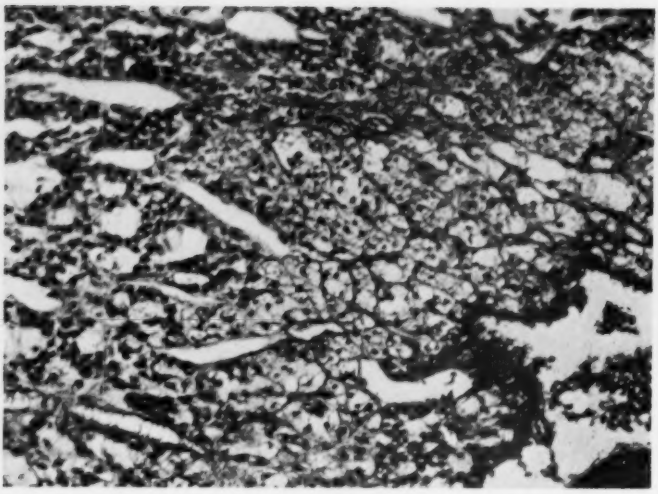

Fig. 4.—Histologic appearance of the left adrenocortical tumor (surgical specimen).

the blood pressure, and the Robinson-Power-Kepler test were normal. The fasting blood sugar, however, was slightly lower than normal, and the oral glucose tolerance test was flat (Fig. 2, Curve *B*). When this test was repeated two hours after the oral administration of 50 mg. cortisone, the following values were obtained: fasting, 71 mg. per 100 cc.; 30 minutes after the ingestion of 100 gm. of glucose, 133 mg. per 100 cc.; 60 minutes, 143 mg. per 100 cc.; 2½ hours, 134 mg. per 100 cc. The rise of the blood sugar following the intravenous glucose tolerance test was somewhat less than in normals. The urinary steroid assays performed during this phase (see Hormone Studies) confirmed the clinical impression of hypoadrenalism. The hypoadrenal state subsided gradually, and no substitution therapy was necessary. Physical examination as well as laboratory studies performed repeatedly up to three years following the operation revealed no abnormalities.

STAGE 3.—*Emergence of Virilizing Signs Due to Local Recurrence and Widespread Metastases*

The patient returned three and one-half years after the removal of the adrenal tumor because of recurrent facial hair growth and increasing irritability for which she sought psychiatric help. The menstrual periods were regular up to two months prior to the second admission. She had marked facial hirsutism; masculine hair distribution of arms, chest, and abdomen; a "moon" facies, and enlargement of the clitoris. No striae or acne were present. The blood pressure was 170/110 mm. Hg; the liver was enlarged, extended 4-5 fingerbreadths below the right costal margin, and was irregular and nodular, consistent with liver metastases. A presacral air insufflation disclosed multiple masses in the suprarenal area, indicative of recurrent adrenal malignancy. The roentgenograms of the chest and skull were normal; those of the dorsolumbar spine showed mild osteoporosis, but no bone metastases were demonstrated.

The laboratory tests of this phase are listed in Table 1. The oral glucose tolerance curve was again of the diabetic type (Fig. 2, Curve *C*). The serum calcium ranged from 10.6-11.4 mg. per 100 cc. The alkaline phosphatase was moderately elevated.

It was decided to reexplore this patient. A 150 mg. dose of cortisone was given orally on the day

TABLE 1.—*Clinical Laboratory Tests (Average Values)*

Test	Preoperative	Mo. After Operation		Metastatic Phase
		5	17	
Blood sugar mg./100 cc.	92	69	65	63
Ca, mg./100 cc.	11.6	10.8	10.7	11.0
Alkaline phosphatase, Bodansky units	4.4	4.7	4.1	7.0
P, mg./100 cc.	3.2	4.1	3.3	3.1
Na, mEq./L.	141	134	140	142
Cl, mEq./L.	102	101	102	99
K, mEq./L.	4.2	4.0	4.7	4.7
CO_2, mEq./L.	29.3	23.2	24.6	26.5
BUN, mg./100 cc.	13.6	12.7	15.8	18.2
Hb., gm./100 cc.	14.4	11.9	10.8	15.9
RBC, million/cu. mm.	4.8	4.0	3.6	3.6
WBC	11,700	7700	7900	11,200
Differential WBC count	1-3 Myelocytes and metamyelocytes	Normal	Normal	90% polymorphonuclear cells, 2% young forms
Eosinophils	42	164	--	0
BMR, %	+42	+1	—4	—5
BP, mm. Hg	170/100	140/90	125/80	170/110
ECG	Inverted T_1	Normal	—	Left ventricular hypertrophy
Body weight, kg.	51.8	50.9	50.0	51.4

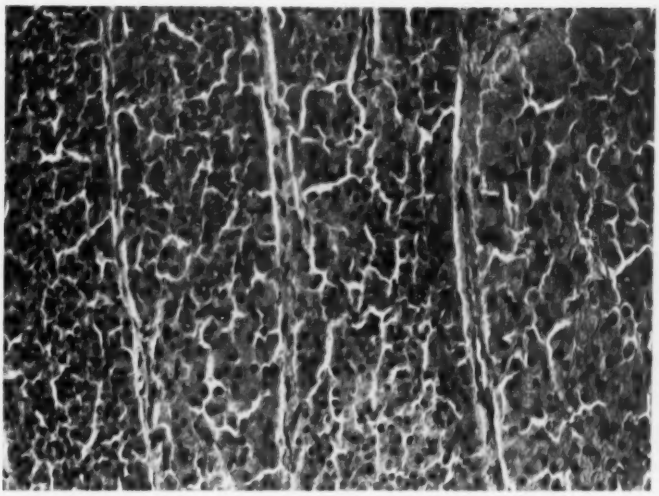

Fig. 5. — Microscopic appearance of the metastatic adrenocortical carcinoma (section of liver metastases).

prior to operation. An exploratory operation through a left lumbar incision was performed in July, 1955, and multiple huge nodular tumor masses were identified in the retroperitoneal space, especially in the area of the left adrenal. Also numerous periaortic lymph nodes were found to be involved by tumor. Approximately 200 gm. of this recurrent tumor were removed together with the left kidney. The microscopic examination showed this tumor to be carcinoma of adrenal cortical origin (Fig. 5). Cortisone was continued postoperatively, and the dose was gradually decreased. Fifteen days postoperatively, when the patient received 25 mg. of cortisone per day, the temperature rose to 103 F and the blood pressure dropped to 95/70. This was thought to be due to hypoadrenocorticism. The dose of cortisone was increased, resulting in prompt improvement. Six weeks after the operation cortisone was gradually withdrawn.

Eighteen days after the withdrawal of cortisone Amphenone was administered for ten days. The single dose of Amphenone varied from 0.75 to 0.5 gm. and was given every three hours. The daily dose of Amphenone and the changes of blood pressure and temperature are listed in Table 2. Because of drowsiness, a rise in temperature, and a slight decrease of the blood pressure the dose of Amphenone was decreased on the second day. Since the blood pressure further decreased and the temperature rose to 103 F, Amphenone was omitted for one day on the third day of treatment. The patient was drowsy most of the time during the course of Amphenone, and her dietary intake had considerably decreased. The hepatic metastases became tender and appeared to decrease in size. The temperature remained elevated and rose to 104 F on the 10th day of treatment. Amphenone was discontinued; the patient was given sulfisoxazole (Gantrisin) because a urine culture was positive for Escherichia coli. However, the temperature became normal within 12 hours after discontinuation of Amphenone, and the blood pressure rose to 150/100 mm. Hg.

Ten days after Amphenone therapy the patient had severe abdominal pain, and peritonitis secondary to a perforated peptic ulcer was suspected. Because of the widespread metastatic disease and the patient's poor condition she was treated conservatively. She improved on the medical regimen. Two weeks later she became icteric; her course was rapidly downhill. Two days prior to her death she vomited large amounts of blood. Death occurred four years after the initial diagnosis of Cushing's syndrome was made.

TABLE 2.—*Changes of Blood Pressure and Temperature During Amphenone Therapy*

	Pre-Amphenone	Days of Amphenone Administration									
		1	2	3	4	5	6	7	8	9	10
Amphenone, gm./day	0	6	3.75	0	3.5	4	4	4	4	4	3.5
Temperature *	Normal for 30 days	100.6	103.6	103.0	101.2	100.4	99.2	101.2	101.8	102.2	104.0
Blood pressure †	160/100 - 180/100	150/110	150/105	110/90	120/90	130/85	115/90	135/90	120/90	120/90	125/90

* Highest reading of the day.
† Lowest reading of the day.

TABLE 3.—*Metabolic Balances*

Stage of Disease	Duration of Study, Days	Body Wt. Kg.	Nitrogen, Mg./24 Hr.			Phosphorus, Mg./24 Hr.			Calcium, Mg./24 Hr.			Sodium, mEq./24 Hr.			Potassium, mEq./24 Hr.		
			Intake	Urine	Stool	Bal.	Intake	Urine	Stool	Bal.	Intake	Urine	Stool	Bal.	Intake	Urine	Stool	Bal.
Preoperative	18	51.2	8,439	9,420	988	—1,979	660	541	246	—129	162	201	215	—254	88.0	74.8	1.2	+12.0	56.2	52.9	7.0	—3.7
5 Mo. postoperative	8	49.8	10,850	8,386	761	+1,703	758	439	168	+151	180	81	176	—77	107.6	99.3	1.6	+ 6.7	63.4	52.5	4.5	+7.4
Metastatic phase	10	50.6	10,672	10,834	1,260	—1,422	702	682	208	—188	147	260	205	—318	137.5	119.8	4.0	+13.7	49.6	43.5	12.7	—6.6
Amphenone therapy	10	—	3,096	6,642	685	—4,241	258	371	127	—240	78	128	179	—228	66.5	24.6	8.7	+33.2	19.7	25.7	4.8	—10.8

Necropsy revealed widespread metastases from an adrenal cortical carcinoma. The liver weighed 2800 gm. and was studded with multiple yellow nodules with elevated brown edges, simulating adrenal tissue. Similar masses were present in the retroperitoneal space. There was one small tumor nodule in the lung parenchyma. In the first part of the duodenum there was a perforated ulcer, 2.5 cm. in diameter, leading into a walled-off cavity containing 200 ml. of blood. The right adrenal weighed 8 gm. and showed no gross or microscopic abnormalities. The right kidney weighed 175 gm. and showed no abnormalities. The thyroid gland weighed 25 gm.; histologically it showed no abnormal findings. The pelvic mass was a large fibromyoma of the uterus. The sections of the vertebrae, sternum, and ribs showed thinning and considerable atrophy of the trabeculae, but there was no tumor involvement of bone. Three parathyroid glands were identified; they did not show any gross or microscopic abnormality. Permission for the examination of the brain could not be obtained.

II. Metabolic Study

The patient was studied on the metabolic research ward during each of the three stages of the disease. She received an analyzed low-calcium diet containing approximately 150 mg. of calcium and 600 mg. of phosphorus per day.[9] Balances of nitrogen, calcium, phosphorus, sodium, and potassium were determined (Table 3). Calcium tolerance tests were performed in each stage of the disease (Table 4).

The diet and the excreta were analyzed for nitrogen, calcium, phosphorus, sodium, and potassium on aliquots of each six-day metabolic period. Nitrogen was determined by the Kjeldahl method; phosphorus, by the method of Fiske and Subbarow[10]; urinary calcium, by the method of Shohl and Pedley.[11] Calcium of the diet and stool was determined on acid ashed aliquots of six-day metabolic pools. Sodium and potassium of the diet and excreta were determined on aliquots of six-day pools by the flame photometer.

STAGE 1.—This study lasted 18 days. On an average daily intake of 1.3 gm. of protein per kilogram the nitrogen balance was negative. Also, the phosphorus, calcium, and potassium balances were negative. The

TABLE 4.—*Calcium Tolerance Tests Performed in the Three Stages of the Disease*

Stage of Disease		Serum		Urinary Calcium, Mg./Day		Ca Retention, % of Ca Injected‡	Urinary Phosphorus, Mg./Day	
		Ca, Mg. /100 cc.	P, Mg. /100 cc.	Spontaneous*	Induced†		Spontaneous*	Induced†
Preoperative		11.9	3.0	204	548	23	826	514
		11.1	3.9	218	456	47	601	528
Mo. after operation	5	11.3	4.1	44	122	83	444	265
	17	9.5	3.6	27	89	86	526	231
	17½	10.7	3.4	25	119	79	469	321
Metastatic phase		11.7	3.4	107	338	51	830	668
		10.0§	3.3	330	543	55	739	746

* Day before test.
† Day of test.
‡ 50 ml. of 10% calcium gluconate (469 mg. Ca^{++}) was infused.
§ Performed 4½ mo. after the first test in the metastatic phase.

intravenous calcium tolerance test was performed twice.[3,12,13] This test revealed poor retention of the infused calcium; the urinary phosphorus excretion decreased on the day of the calcium infusion in both tests.

STAGE 2.—Five months after the removal of the adrenal tumor the balances of nitrogen, phosphorus, and potassium became positive. The calcium balance became normal owing to a marked decrease of urinary calcium excretion. The calcium tolerance test showed a striking change; the spontaneous (preinfusion) and the induced (day of infusion) calciuria decreased considerably, and the retention of the infused calcium increased to levels which were even higher than observed in normals. The test repeated 17 and 17½ months postoperatively showed principally the same results. The urinary phosphorus decreased considerably on the days of the tests.

STAGE 3.—The calcium tolerance test gave results similar to those obtained in the two tests prior to operation, although the urinary calcium was not as high as in Stage 1. However, the calcium retention decreased again to low levels similar to the preoperative phase. A repeat calcium tolerance test performed two months later gave similar results, although the urinary calcium had further increased to 330 mg. per 24 hours. It is of interest to note that the phosphaturia did not decrease during this latter test, but increased by a few milligrams. Metabolic studies revealed that the balances of nitrogen, phosphorus, calcium, and potassium became again negative and were similar to those of Stage 1. The negative calcium balance was mainly due to increase of the urinary calcium excretion.

An attempt was made to study the metabolism of this patient during the 10-day period of Amphenone therapy. The data obtained are listed in Table 3, although their significance is very questionable, since the dietary intake decreased progressively, and the patient's clinical state became too critical to measure balances reliably.

III. Hormone Studies

(*a*) *Methods*

Twenty-one separate urine collection periods of this patient were studied in the time interval from 1951 to 1955. Of this total, detailed examinations of individual urinary steroids were made in eight periods. In Stage 1, Period 1, a four-day collection before removal of the adrenocortical tumor. In Stage 2, Period 2, a 13-day collection five months after removal of the tumor. In Stage 3, Period 5, a four-day control obtained after recurrence of metastatic disease; Period 8, a one-day period representing the third day of corticotropin administration (20 mg. per day, intravenously); approximately 6 weeks later, Period 11, a two-day collection was obtained while the patient received a maintainance dose of 62 mg. of cortisone orally per day; Period 13 represents a five-day collection made 3 weeks after cortisone was discontinued; Period 16, a three-day collection of Days 7 through 9 during the 10 days of treatment with Amphenone (4 gm. per day); Period 18 represents a one-day collection 8 days after Amphenone was discontinued.

All collections were complete and were processed immediately following enzymatic and acid hydrolysis of urinary steroid conjugates. Isolation and quantitation of individual steroid metabolites was

TABLE 5.—*Steroid Hormone Production During the Period 1951-1955* *

Compounds	Pre-operative	Post-operative 5 Mo.	Metastatic Phase					
			Control	Corti-cotropin	Cortisone	Post cortisone	Amphenone	Post-Amphenone
11-Ketoetiocholanolone	1.9	0.5	5.8	12.2	3.8	5.3	1.0	6.4
11-Hydroxyetiocholanolone	5.7	0.1	6.3	12.1	4.6	5.6	1.8	6.1
11-Hydroxyandrosterone	5.6	0.1	9.2	15.8	6.1	6.6	2.1	8.9
Etiocholanolone	8.4	0.3	61.9	85.1	40.5	62.1	25.2	90.0
Androsterone	1.3	0.5	17.2	29.3	17.1	24.1	9.1	31.0
Dehydroisoandrosterone	1.0	0.1	87.3	128.2	45.2	178.0	1.3	118.0
Date	12/51	4/52	7/55	7/55	9/55	10/55	10/55	10/55
Period	1	2	5	8	11	13	16	18

*Values expressed in milligrams per 24 hr.

done, employing the extensive methodology described previously.[14,15]

(*b*) *Results*

The values for each of the isolated compounds are reported in milligrams per 24 hours in Table 5. The three 11-oxygenated steroids isolated were as follows: 11-hydroxyandrosterone (3*α*, 11*β*-dihydroxyandrostane-17-one), 11-hydroxyetiocholanolone (3*α*, 11*β*-dihydroxyetiocholane-17-one), and 11-ketoetiocholanolone (3*α*-hydroxyetiocholane-11,17-dione). The three 11-desoxysteroids isolated were androsterone (3*α*-hydroxyandrostane-17-one), etiocholanolone (3*α*-hydroxyetiocholane-17-one) and dehydroisoandrosterone (3*β*-hydroxy-Δ^5-androstene-17-one).

The preoperative control (Period 1) reveals normal levels of androsterone and dehydroisoandrosterone but increased amounts of the 11-oxygenated steroids and etiocholanolone compared with normal women.[16] After surgical removal of the tumor (Period 2), the excessive amounts of these steroids disappeared; indeed, the 11-oxygenated compounds dropped to levels below normal. With recurrence of symptoms of hyperadrenalism secondary to functional metastases a striking alteration in the steroid excretion pattern occurred (Period 5). The 11-oxygenated steroids returned to excessive levels and were higher than those seen in the preoperative period (Period 1); there was a marked increase in androsterone and etiocholanolone production, and most striking of all was the pronounced elevation in dehydroisoandrosterone, a steroid which now exceeded in amount any of the other compounds.

Under corticotropin stimulation (Period 8), a significant increase in tumor steroidogenesis occurred. Attention is called in particular to the very marked increase in dehydroisoandrosterone. This increase alone, quite apart from that exhibited by the other steroids, is unequivocal evidence of the capacity of this neoplasm to respond to adrenocorticotropin.

The steroid response to exogenous cortisone (Period 11) must be considered in relation to the control periods several weeks preceding (Period 5) and following (Period 13) the administration of this hormone, since a more immediate control could not be obtained. With this qualification, exogenous cortisone seems to have induced a significant depression of tumor steroidogenesis. This depression of steroid production was manifest particularly in the amounts of the 11-desoxysteroids, since the 11-oxygenated compounds include the degradation products of administered cortisone.

During the administration of Amphenone (Period 16), a striking reduction in steroid production by the tumor occurred. The 11-oxygenated steroids dropped significantly, and, for reasons discussed previously,[5] the levels reported here are undoubtedly higher than the true values. There was a marked decrease in dehydroisoandrosterone as well, and androsterone and etiocholanolone diminished appreciably. After the end of Amphenone administration (Period 18) the tumor reverted to the previous high level of steroid production.

Comment

Many case reports and reviews have appeared on Cushing's syndrome and Cushing's disease since pituitary basophilism [17] was first described in 1932. Plotz et al.,[18] Soffer et al.,[20] and Cope et al.[21] have reported on large series of such patients, and the normal and the pathologic physiology of the human adrenal cortex have recently been reviewed.[19,22] Bilateral adrenal hyperplasia is the most frequent cause of Cushing's syndrome, while benign or malignant tumors of the adrenal cortex occur in less than one-third of such patients.[23]

Early diagnosis and definitive therapy are of prime importance in all cases, since an approximately 50% mortality was reported to occur within five years of the known onset of the disease; cardiovascular complications are the principal cause of death in young adults with Cushing's syndrome.[18] The fully developed clinical entity of Cushing's syndrome can easily be recognized. Patients with less overt manifestations, however, present difficult diagnostic problems. For instance, Browne et al.[24] described a patient in whom nephrolithiasis was the initial clinical manifestation of Cushing's syndrome, the typical features of which developed several months later. Cope reported a patient with an adrenocortical carcinoma and increased 17-ketosteroid excretions in whom there were no clinical symptoms other than those referable to thyrotoxicosis.[25] Soffer reported a 40-year-old man with a functioning adrenocortical carcinoma whose only presenting symptom was edema.[20] Psychologic changes may also precede the somatic manifestations.[18,23]

Clinical manifestations in the patient reported here were initially not very pronounced. There had been a slight increase in long-standing mild hypertrichosis, as well as cessation of menses preceding admission for study. In addition mild hypertension and osteoporosis were noted. There was no significant alteration in the character or distribution of body tissue, and there were no striae, plethora, easy bruisability, or other characteristic skin changes. In contrast to these minimal clinical expressions of adrenocortical disease, major hormonal and metabolic derangements existed which gave evidence of significant hyperfunction of this gland. Roentgenographic demonstration of an adrenal tumor confirmed these observations.

Several metabolic studies have previously been reported on patients with Cushing's syndrome. Cushing cites a study of Aub on a 15-year-old girl with pituitary basophilism who had an abnormally high urinary calcium excretion although the serum calcium was normal.[26] Albright et al.[27,28] Kepler et al.,[29,30] and Soffer et al.[31] have studied metabolic balances and the effects of therapy in patients with Cushing's syndrome. Carter et al.[32] noted negative nitrogen, calcium, and phosphorus balances in only 3 of 13 and elevated 17-ketosteroid excretions in only 8 of 16 such patients with advanced disease. Metabolic studies performed in the patient reported here revealed negative balances of nitrogen, phosphorus, potassium, and calcium similar to the results of balance studies of other investigators.[29-34]

The abnormalities of the skeletal system and of bone metabolism which may occur in Cushing's syndrome warrant comment. Although osteoporosis and even collapse of vertebrae occur frequently and are readily diagnosed in the advanced stages of the disease,[18,20] the recognition of early osteoporosis presents a difficult problem. The roentgenograhic changes may be minimal, and the serum calcium [18,20] and alkaline phosphatase [18] are usually within normal limits. The increased urinary calcium excretion and the impaired calcium retention demonstrated by the calcium tolerance test [3,12,13] may help establish the early diagnosis of osteoporosis. Indeed, this was true in the patient reported here and in 15 of the 17 patients studied at the New York Hospital, by Carter, Horwith, and Shorr.[35]

The difficulties of prognosis in a patient following removal of an encapsulated adrenal tumor are well illustrated by this case.

TABLE 5.—*Steroid Hormone Production During the Period 1951-1955* *

Compounds	Pre-operative	Post-operative 5 Mo.	Metastatic Phase					
			Control	Corti-cotropin	Cortisone	Post cortisone	Amphenone	Post-Amphenone
11-Ketoetiocholanolone	1.9	0.5	5.8	12.2	3.8	5.3	1.0	6.4
11-Hydroxyetiocholanolone	5.7	0.1	6.3	12.1	4.6	5.6	1.8	6.1
11-Hydroxyandrosterone	5.6	0.1	9.2	15.8	6.1	6.6	2.1	8.9
Etiocholanolone	8.4	0.3	61.9	85.1	40.5	62.1	25.2	90.0
Androsterone	1.3	0.5	17.2	29.3	17.1	24.1	9.1	31.0
Dehydroisoandrosterone	1.0	0.1	87.3	128.2	45.2	178.0	1.3	118.0
Date	12/51	4/52	7/55	7/55	9/55	10/55	10/55	10/55
Period	1	2	5	8	11	13	16	18

*Values expressed in milligrams per 24 hr.

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The difficulties of prognosis in a patient following removal of an encapsulated adrenal tumor are well illustrated by this case.

This patient was free of hyperadrenocorticism for three and one-half years, as evidenced by return of normal menses, reversion of the blood pressure to normal, and studies of urinary steroid excretion. Indeed, there was clinical and biochemical evidence of hypoadrenalism for several months after the operation. Metabolic balances showed a change from the catabolic to the anabolic phase, and the calcium tolerance test showed a reversal to a pattern indicative of the repair of osteoporosis. During the subsequent three and one-half years her clinical course was normal. The ultimate emergence of marked virilization in the terminal, metastatic phase was preceded by several months of psychological disturbances. At this time the menstrual cycle was still normal, and the patient was able to continue full-time employment. With the resurgence of the somatic manifestations of hyperadrenocorticism, the balances of nitrogen, phosphorus, potassium, and calcium again became negative, and the calcium tolerance test reverted to the preoperative pattern.

The suppression of adrenal and thyroid function by Amphenone in animals and in man and the toxicity associated with the administration of this compound have been described.[6-8] The drowsiness, decrease of blood pressure, and the elevation of the temperature observed in this patient are in agreement with observations made in other patients. The histologic changes of the adrenal and thyroid gland noted in experimental animals were not seen in this patient. This is probably due to the fact that the patient died one month after discontinuation of therapy.

The steroid isolation studies in this patient revealed several interesting and significant functional characteristics of this patient's tumor. During the local phase of this neoplasm (Stage 1, Period 1), this patient's steroid excretion pattern was characterized by an increase in the 11-oxygenated metabolites as well as in the 11-desoxy compound etiocholanolone. This combination of derivatives suggests that the principal synthetic activity of this tumor was directed toward the production of hydrocortisone and its 11-desoxy intermediates. The clinical expression of this hyperadrenalism, Cushing's syndrome in a mild form, was consistent with this interpretation of the nature of the excess adrenal hormone. Following surgical removal of the tumor (Stage 2, Period 2), the steroid pattern reverted to that indicative of a low level of endogenous adrenal activity consistent with the period of hypoadrenalism manifested clinically by this patient.

The later development of functionally active metastases in this patient (Stage 3) was associated with a major shift in the character of the excess hormone produced, as well as in its clinical manifestations. There was a marked elevation in the 11-oxygenated steroids during this period. In addition, there was an even more striking increase in steroids lacking the oxygen function at carbon-11. This increase was especially notable with dehydroisoandrosterone, a substance whose production has frequently been noted to be excessive in adrenocortical malignancy.

The change in the character of steroidogenesis during this phase suggests that the production of androgens, or substances intermediate to androgens, predominated. The superposition of masculinizing signs at this time upon the previous clinical status is confirmation of this change in hormone production. Thus, during all three stages of this patient's tumor there were characteristic alterations in its steroid hormone synthetic activity consistent with the clinical manifestations.

The capacity of this tumor to respond to exogenous hormone was another significant functional characteristic demonstrated in this study. The response to corticotropin was unequivocal and particularly striking insofar as the production of dehydroisoandrosterone was concerned. As noted above, suppression of the functional capacity of the tumor produced by cortisone must be pre-

sumed on the basis of a comparison of steroid production during this period with steroid production during Periods 5 and 13. This comparison strongly suggests that such suppression did, in fact, take place.

The response to Amphenone makes it evident that a nonhormonal influence could be brought to bear upon this tumor, as well. This suppression of steroidogenesis produced by this chemotherapeutic agent was profound (Period 16), although steroid production returned to the previous level when the compound was discontinued (Period 18). This rapid return to a high level of steroid production implies that Amphenone has a functional influence rather than a lethal effect on the tumor, which is in keeping with the results of previous studies of the effect of this agent on adrenal function.[8,36]

These results thus establish clearly that unresponsiveness to exogenous or endogenous hormonal control cannot be considered a distinguishing characteristic of adrenocortical malignancy. The necessity for individual and detailed consideration of the functional status of these tumors is therefore apparent. The observations on the suppressive influence of Amphenone emphasize further the possibility of a chemotherapeutic approach to the control of tumors of this type and serve to stimulate a search for related substances with less general toxicity and more prolonged effectiveness.

Summary

The clinical, metabolic, and hormonal changes in a patient with hyperadrenocorticism due to adrenocortical carcinoma were studied over a period of four years. During its initial localized phase this tumor produced excessive amounts of steroid of a type consistent with the associated clinical and metabolic expressions of mild Cushing's syndrome. During its metastatic phase, significant alterations in hormone production occurred in keeping with the superposition of marked signs of virilization upon the previous clinical status.

At a time when the tumor was widely disseminated it was still possible to demonstrate some degree of control over its functional status by corticotropin and cortisone and by the chemotherapeutic agent Amphenone.

Dr. H. M. Zimmerman, Chief, Division of Laboratories, and his staff cooperated in this study and gave permission for use of the pathological material.

Montefiore Hospital, 210th St. & Bainbridge Ave. (67).

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Polyps and Carcinoma of the Colon

M. B. GOLDGRABER, M.D., and J. B. KIRSNER, M.D., Ph.D., Chicago

Introduction

Carcinoma of the large bowel has been found significantly more often in chronic ulcerative colitis than in the general population of the same age, sex, and race.[1] Before this conclusion was reached a variety of questions had to be answered: 1. What is the "normal" frequency of polyps and carcinoma of the large bowel? 2. What are the possibilities of malignant transformation of an adenomatous polyp? 3. What are the chances that inflammatory pseudopolyps could undergo further evolution into an adenoma and into a malignant growth? The information obtained from the literature on this important subject has been summarized in this brief review.

There is a continued interest in the nature and cause of polyps of the large intestine.[2-7] The frequency of polyps on routine proctoscopic examinations at the University of Chicago Clinics was 5.4%.[8] Single polyps were found in 88% of the cases; multiple polyps, in 12%. Recurrences occurred in 20% of cases in the single-polyp group and 44% in the multiple-polyp group. Carcinoma of the large intestine was five times more frequent in the polyp group than in those without polyps (10.4% versus 2.1%). In the group with more than one polyp the frequency of carcinoma was 20%. An important follow-up study is in progress, and the low incidence of cancer of the colon in this group (none in 1954 and two in 1955) reflects the effective program of cancer prevention. In a study of 7000 autopsies [9] there were only 15 polyps in the small bowel, as compared with 196 in the colon and rectum. The important question arises as to why the small bowel mucosa is only rarely the site of polyps and cancer and whether the factors of fluid content, alkalinity, sterility, and the absence of abrupt bends are of significance and to what degree is a matter of pure speculation, as pointed out by Brown and Nalefski.[10]

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Department of Medicine, The University of Chicago.

Pathogenesis of Polyps

Virchow considered polyps a hyperplastic response to inflammation. Ribbert thought they might arise from misplaced embryonic remnants in the wall of the bowel, and Verse, cited by Coffey and Bargen,[11] thought of a congenital predisposition together with chronic irritation. Dukes [12] made a detailed description of the various stages of adenoma formation. The operative factor would be a more lively multiplication of epithelial cells within a certain area. What brings about this abnormal proliferation is, according to the author, an "unprofitable question." Another theory concerns the formation of adenomata from submucous structures, such as lymph follicles. Bargen [13] considered cancer of the colon a reaction to prolonged irritation and implicated the lymphocytic aggregates disrupting the continuity of the muscularis mucosae, causing atypical cell proliferations; this would produce prolapses of glandular elements into the ruptured follicle. He assumed that a disturbed environmental relationship is created in this manner, and this would be responsible for the potential malignancy of that particular region. Schultze [14] considered the prolapses of glandular elements as variations of evolution, but as he saw such occurrences in the region

of cancer be admitted that such deep-seated crypts could develop malignant neoformation "under circumstances." Valdes-Dapena,[15] in a recent study, emphasized the importance of submucosal localized edemas as the first change in tiny polyps. The epithelial changes on top of the displaced mucosa would supervene later. These would consist in changes near the surface with a pattern reminding of a villous papilloma. This work, however, requires further confirmation.

Experimental Production of Polyps and and Intestinal Carcinoma

The experimental production of polyps has been reported repeatedly.[16,17] Polyps were produced in rabbit colons during an attempt to induce experimental ulcerative colitis.[18] Spontaneous intestinal cancer is rare in lower animals.[19] In 142,000 necropsies in Slye stock mice there were only one adenocarcinoma of the cecum and one in a prolapsed rectum. Sarcomas were more frequent, with 8 of 18 malignancies observed. These data suggest that the positive results obtained in experimental carcinogenesis are unlikely to be due to tumors, which could occur spontaneously. Cancer of the colon was induced experimentally in mice by injection of cholanthrene directly into the wall of the cecum.[20] Recently Nowell et al.[21] applied fast-neutron radiation to mice and obtained 17 carcinomas in 63 mice surviving 13 to 16 months after the irradiation; 11 tumors were located in the cecum, and 6, in the small bowel. There was an associated alternation of atrophic and hyperplastic areas, together with these tumors, which were highly invasive. Horava[22] recently reported the results of application of cotton strings saturated with methylcholanthrene to the colonic mucosa. Sections taken 15 weeks after start of the experiment demonstrated hyperplasia of the mucosa, dysplasia of cells, and inflammation. There was invasion of the submucosa by islands of nonsecreting dysplastic columnar cells similar to "Schultze pictures." In Horava's experiments 21 of 72 rats had inflammatory lesions, 13 had dysplasia, 9 had carcinoma in situ, and 19 had invasive carcinoma. Berenblum et al.,[23] using the same methods, could not obtain epithelial tumors and concluded that the rectal mucosa in mice is not responsive to the carcinogenic action of methylcholanthrene. They obtained instead malignant tumors of mesenchymal tissues, the majority of which were invasive. It is of interest that Lushbaugh and Hackett[24] obtained with lubricating oil, not containing carcinogens, foci of hyperplasia in the colon of mice and in one case an adenocarcinoma with metastases to the regional lymph nodes. When the same animals were given a diet deficient in folic acid, infiltrating lesions of the mucosa were obtained in half of the treated animals.

Adenoma—A Premalignant Lesion

There is no direct evidence of malignant transformation of an adenomatous polyp into carcinoma, but such evidence is very difficult to obtain, as pointed out by Rider, et al.[8] The circumstantial evidence of malignant transformation of polyps into carcinoma is based on (1) close parallelism of location; (2) close parallelism as to age and sex distribution; (3) frequency of association between polyps and carcinoma; (4) the finding of patients with familial polyposis dying of cancer; (5) presence of carcinoma in recurrences of a benign polyp.

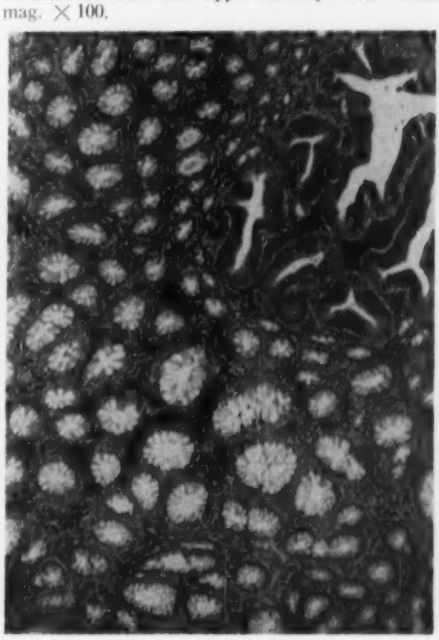
The difficulty in diagnosing malignancy in adenomatous polyps is well known, and the divergence of opinion of pathologists as to the requirements for such a diagnosis was well documented in a survey published by Rosenberg,[25] in 1955. Welch et al.[26] also emphasized the differences of opinion regarding atypical adenomatous polyps, carcinoma in situ, and other adenocarcinomas.

The malignant transformation of adenomas has been challenged by several authors: Turnbull and Fisher[27] followed a group of 27 patients: 16 had so-called carcinoma in situ; 11 had superficial carcinoma with invasion of lamina propria without breaking through the muscularis mucosae. None of this group died of recurrence or

metastasis of the original tumor. Fitzgibbon and Rankin [28] divided polyps into three groups similar to the classification made earlier by Schmieden and Westhues.[29] Those of the first group are well differentiated and invariably pedunculeated. Those of the second group have areas of epithelium which failed to differentiate; the third group, disorderly dedifferentiated and rapidly growing, would provide the main source of carcinomatous transformation. Their opinion was that those of Group 1 practically never become malignant. Colvert and Brown [30] published a follow-up study of a group of 117 patients in whom benign polyps were removed and of another group of 43 patients who did not have any treatment for their polyps. The latter group did not develop more carcinomas in five years than the group which had their polyps removed. The authors tend to conclude that polyps do not become malignant with the passage of time. Now, did all these polyps belong to Group 1 of Fitzgibbon and Rankin? If so, how many of the adenomatous polyps belong to this group, and how is this distinguished in advance? These problems do not seem to be solved readily.

On the other hand, there are many authors who accept the concept of malignant transformation of polyps. In Saint's experience [31] some carcinomas occur with adenomatous polyps (36%), but the majority of cancers would arise "per se." This author did not observe malignant changes in adenomas smaller than a walnut. Swinton and Warren [32] felt that 14% of carcinomas could be traced to adenomatous polyps, but Swinton and Counts [33] stated: "The majority of cases (of carcinoma) probably arise in a pre-existing benign mucosal polyp." This is also the opinion of many others.[34-37] Westhues [34] considered that 34% of rectal carcinomas arise from a preexisting polyp in a high degree of probability and altogether 60% of cancers could probably be traced back to adenomas. Helwig,[35] in a study of 1460 autopsies, came to the conclusion that carcinomas of the large bowel rarely develop directly from the mucosa and the majority of them arise from adenomatous polyps. This author could not find in his material any evidence that inflammation is consistently a stimulus and an accompaniment of polyps; this opinion was later quoted to question the possibility of a greater incidence of adenomas in chronic ulcerative colitis. Bacon and Broad [36,37] do not doubt that adenoma is only a stage in development of carcinoma and added to the above mentioned circumstantial evidence an observation that both adenoma and carcinoma have a lower incidence in Negroes. David [38] also assumed a gradual transition from hyperplasia to adenoma and "then proceeding to a less ordered epithelial growth and finally to actual carcinomatous invasion." Buie and Brust,[39] in a follow-up study of 143 cases of solitary adenoma of the rectum and sigmoid, were able to compare a group of 63 untreated cases with 34 treated by electrocoagulation. While no cancer developed in the treated group, four patients died of intestinal carcinoma in the untreated group. These observers believe that the site of carcinoma in their four cases was where adenoma was previously

Fig. 1.—Adenomatous polyp. At the right upper corner the glands are deeply stained and dedifferentiated. Reduced approximately 40% from mag. × 100.



seen. Atwater and Bargen [40] went even further. In a study based on multiple sections from necropsy material and on adequate controls, they gave the opinion that the benign adenomatous polyp is not a defined limited entity but one stage in the pathogenesis of carcinoma. Finally, Smith [41] considers well established the concept that the majority of cancers of the colon, if not all, arise from adenomatous polyps.

In summary, the prevailing opinion is that an adenoma is a transition phase from epithelial hyperplasia to frank carcinoma. There are marked differences in the rate of growth of different adenomas, and the slow-growing polyps may practically never attain a malignant stage. The difficulty lies in the fact that there is no certain way to determine which adenoma is or will be of fast growth and will undergo malignant transformation. A corollary of this view is the unanimous recommendation to remove all intestinal polyps. Figure 1 illustrates an adenomatous polyp with an area of dedifferentiation suggestive of malignant potentialities.

Inflammatory Polyps

Polyps of childhood may belong to the category of inflammatory polyps. According to Bensaude et al.[42] these polyps are characterized by increased amount of interstitial connective tissue and cystic dilatation of glands; the epithelium plays only a minor role in comparison with that in the adenomatous polyps. These authors thought that these polyps of childhood never develop carcinoma. Kerr,[43] nevertheless, had two cases of carcinoma in a group of 100 children with polyps. One had a carcinoma at the age of 24 on top of a mass which protruded from the anus for many years. The other case was that of a boy with an obstructing lesion of the colon which was found at laparotomy to be perforated and to have metastasized to the liver. Polyps of inflammatory character are not infrequently encountered also in adults without signs of active colonic inflammation (Fig. 2). Inflammatory polyps have developed also during injury of the colon in experimental ulcerative colitis.[18]

Fig. 2.—Inflammatory polyp in a woman 27 years old without history of large-bowel disease. Reduced approximately 40% from mag. × 32.

Pseudopolyps of Ulcerative Colitis

There is frequently in ulcerative colitis deep ulceration, leaving islands of mucosa which protrude into the lumen like sessile polyps. Sometimes a piling up of tissue develops, with formation of bridges, buried epithelium, and considerable distortion of morphology. These are not always expression of true hyperplasia, but in the course of time true adenomas may develop. Bargen [44] believes that in ulcerative colitis a transition from adenomatous change into malignancy may occur. Such a development also is accepted by other observers.[45-48] Wheeler [46] noted the association of ulcerative colitis with polyps which ultimately leads to carcinoma and, therefore, advocated colectomy. Buie [47] had observed "little tumors" in the inflamed colon to become extensive and involve the entire colon and to form adenomacarcinomatous tumors of the most virulent type. Hurst [48] also was positive concerning the malignant outcome of pseudopolyps in ulcerative colitis. Sawyer [49] thinks

that polyps associated with ulcerative colitis are identical with other types of polyps when well developed. They have definite adenomatous characteristics with a high malignant potential, especially in the healing phase of the surrounding mucosa. Wesson and Bargen [50] observed hyperplasia and adenomatous changes in islands and strands of diseased mucosa left after ulcerations in the colon, and carcinoma would develop in a high proportion of cases (up to 25%). Ricketts and Palmer [51] also stress the variable aspect of pseudopolyps in ulcerative colitis; some will be only islands of mucosa; others will have metaplastic appearance, and in others true neoplasia may ensue. David [38] also emphasized the fact that it is difficult to prove the malignant transformation of inflammatory polyps of ulcerative colitis; nevertheless, on the basis on personal experience, he felt that this occurrence "is more than of ordinary interest." The opposite view was taken by Swinton and Warren,[32] who apparently have never observed the polypoid changes seen in ulcerative colitis progress to a malignant stage. Figure 3 illustrates an inflammatory pseudopolyp with several glands with obvious dedifferentiation.

In summary, the majority of observers believe that an inflammatory pseudopolyp may become malignant, but the evidence for this transition is very difficult to obtain. A statistical study of polypoid changes in ulcerative colitis as compared with a normally occurring incidence of polyps is yet to be made.

The Size of Polyps and Carcinoma

Cain and Bensaude [52] studied a group of cases with very small cancers protruding very slightly above the intestinal mucosa. In their last two cases there was evidence that the cancer arose from the bottom of Lieberkühn's crypts; the integrity of the more superficial layers remained well preserved. This mode of cancer formation seems rare. The authors also admitted that cancers arising from polyps were better studied but that their numerical importance was unknown. Raven [53] also reported an early case of carcinoma still limited to the bottom of the crypts, with a cap of lymphocytes surrounding the newly formed acini. Weingarten and Turell [54] found carcinoma in tiny excrescences 3 mm. in diameter and stressed the fact that small size of polyps is not a guarantee against carcinoma. More recently, Stearns and Deddish [55] did not find any correlation between the size of cancer of the rectum and sigmoid and its prognosis. Conversely, penetration of the bowel wall and lymph node metastases were

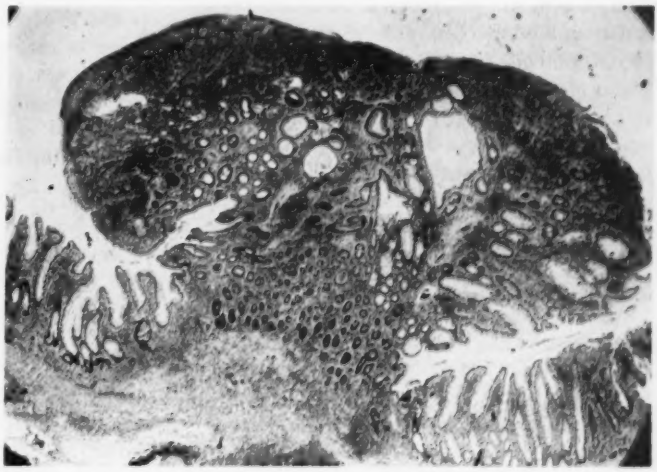


Fig. 3.—Inflammatory pseudopolyp. Note the fibrovascular layer at the periphery. Some of the glands are dilated; others are secreting mucus; some of them are atypical. Reduced approximately ⅓ from mag. × 45.

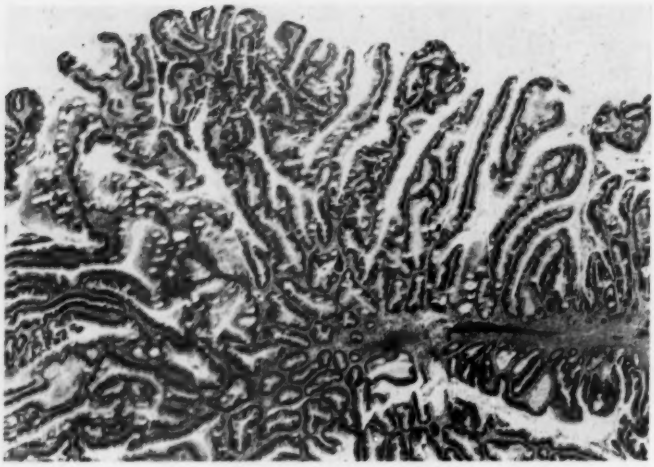


Fig. 4.—Papilloma of rectosigmoid. Reduced approximately ⅓ from mag. ×23.

essentially the same, regardless of the size of the primary tumor.

Papilloma Versus Adenoma

Dukes [56] studied the modalities of papillomatous development and found no difference in the liability to malignancy in papillomas as compared with adenomas. Sunderland and Binkley [57] studied 48 cases of papillomas and separated them into a special entity. The main features of papillomas would be (1) their relative rarity (13.9% of adenomatous polyps); (2) multiple recurrence; (3) more frequent association with carcinoma (in their group, carcinoma in situ was found in 54% of cases, and 19 of 33 developed invasive carcinoma); (4) all but one were located in the rectum. Ewing [58] carefully described the morphology of papillomas and admitted also a pedunculated variety. He stressed also the clinical feature of mucous discharge and the difficulty of detection by touch or by endoscopy. As to the prognosis, the author recommended treating these tumors with "the greatest respect." Gabriel [59] advocated radical surgery for papillomas as the only prospect for permanent cure. Freund [60] had 20 cases; two of them were malignant, requiring an anterior-perineal resection; two developed malignancy later, and two others were found inoperable. Thirteen of their group had a prolonged follow-up and were apparently cured. Bacon et al.[61] studied a group of 28 cases seen in a five-year period. Only one lesion was in the transverse colon; all the others were in the rectum and rectosigmoid. Thirty-eight per cent of these cases showed atypia. Five had carcinoma in situ, and four, frank carcinoma. Lee and Kay,[62] in a recent study of six cases, came to the conclusion that there is little place for conservatism in these unpredictable neoplasms. Ortmayer [63] found 8 papillomas in a group of 174 polyps, but a separate group of 34 had mixed features of adenomas and papillomas. There were no gross criteria by which a benign polyp could be differentiated from a carcinoma. Only ulcerative lesions could be predicted as carcinomas on the base of inspection alone. Figure 3 illustrates a well-differentiated villous papilloma.

Familial Polyposis

Otani and Snapper [64] suggested that the increased frequency of carcinoma in ulcerative colitis might derive from misdiagnosed cases of familial polyposis. However, this is a very rare disease [65-68]; fewer than 10 cases were found in the files of The University of Chicago. Mayo and Wakefield [65] found a frequency of 0.04%, compared with 4% of polyps. Familial polyposis affects males and females,[69] and either may transmit the dis-

ease. In 50% of cases there is a failure to demonstrate a familial history, probably because of the recessive type of gene involved.[70] In some rare cases, there may be polyps from the cardia through the cecum.[71] Some cases may have associated hard or soft subcutaneous tumors, cartilaginous exostoses, or osteomas.[72,73] Others may be associated with melanin pigment spots in and around the mouth.[74] There are cases of the segmental type, and polyps may appear at unpredictable times.[67] The fact that most patients with multiple polyposis die of cancer is one of the bases on which the assumption of malignant transformation of adenomas rests. There is no doubt in most observers' minds that multiple polyposis is a hereditary disease. What about the cases of discrete polyps? Recently, a study [75] was made in which 6 of 24 members of a second generation died of colonic malignancy; 25 of 55 members of a later generation had polyps at proctoscopic examination, a frequency of 45%. This might suggest that discrete polyps may also have a hereditary factor, as suggested long ago by Verse, cited by Plenk.[72]

Miscellaneous Problems

Cole [76] suggested recently that polyps of the large bowel might be on the increase. More of them were seen in the operative room, and more were found in the autopsy records of recent years. In order to check this possibility a quick investigation was made [77] into the frequency of polyps in a sample of patients examined proctoscopically at The University of Chicago Clinics in the period September, 1955, to January, 1957. In this group of 738 patients there were 40 polyps, a frequency of 5.4%, exactly similar to that found by Rider et al.[8] in patients examined during the years 1947 to 1951.

Nevertheless, varying incidence of polyps in relation to unknown factors cannot be excluded. Diamond [78] found in alcoholics sigmoidoscopically demonstrated polyps in a frequency fourfold that found in the nonalcoholic group. Steiner,[79] in a recent study, found that cancer of the esophagus was associated with higher frequencies of history of heavy alcohol consumption and polyps of the large intestine than those found in the control groups. How alcoholism could act as incitement to the development of polyps of the large bowel is quite obscure, but these observations would suggest more studies on this subject.

Summary and Conclusions

The origin of polyps of the intestine is quite obscure. Polyps and carcinomas of the intestine may be produced experimentally if an adequate stimulus is applied and the animal survives long enough to develop the tumor.

The prevailing opinion is that adenomas do undergo malignant transformation, but in individual cases the rate of this transition is unknown and unpredictable.

Inflammatory pseudopolyps, according to most observers, undergo adenomatous changes, and the subsequent course is that of this latter type of epithelial growth.

The size of malignant tumors is not well correlated with their degree of invasiveness.

Department of Medicine, The University of Chicago (37).

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A. M. A. ARCHIVES OF INTERNAL MEDICINE, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

The History of the Use of Iodine in Toxic Diffuse Goiter (Graves' Disease)

ARTHUR L. BLOOMFIELD, M.D., San Francisco

It was Charles Coindet, a Swiss physician, who first used iodine in the treatment of goiter.[1] "Up to the present burnt sponge (*l'éponge calcinée*) has been the basis of all the remedies which have had any success against goiter. Arnold of Villanova [13th century] made this known. . . . What then is the substance in the sponge which works so specifically against goiter? It seemed probable to me that it was iodine: I was confirmed in this opinion when I learned that Mr. Fife of Edinburgh had found iodine in sponges towards the end of 1819 [*]; within six months I have already verified its surprising effects in this malady." Working with Lugol in Paris[2] Coindet introduced hydriodic acid and potassium and sodium iodide. He found that certain solutions of potassium iodide were capable of dissolving more iodine (Lugol's solution) which he felt "augmented the potency of the remedy."

But Coindet really concerns us no further, since he dealt entirely with simple goiter, and there is no suggestion that he treated a case of Graves' disease. However, it is easy to see how iodine came to be tried in the latter, for although Graves' disease was soon to be recognized as a distinct entity, the nature of various goiters was not yet clearly differentiated. Furthermore, when exophthalmic goiter was first described it was regarded as a rare disease; cases were reported singly or in small groups, and the use of iodine, given in a hesitating and haphazard manner, was naturally variously judged in a disease which runs such an uncertain course.

The first mention of the use of iodine in exophthalmic goiter appears to be by von Basedow.[3] "A simultaneously developing strumous swelling of the thyroid gland which allowed one to infer a similar swelling of the cellular tissue behind the eye, invited the use of iodine and digitalis whereby improvement in all respects was brought about."

Interestingly enough those who subsequently reported on the use of iodine in Graves' disease seem to fall into two camps: some doctors were enthusiastic, whereas others were not only indifferent but they regarded iodine as downright harmful and dangerous. On the favorable side were the following doctors:

William Stokes,[4] in his book, has only a brief word: "In one case the thrilling tumour of the neck subsided under the use of iodine." But at a hearing of the commission

Submitted for publication April 13, 1957.

From the Lane Medical Library.

* Iodine was actually discovered in 1812, by B. Courtois (in seaweed), and in 1815 L. J. Gay-Lussac showed that it was an element.

appointed by the Paris Academy to look into the whole question of Graves' disease, on July 22, 1862, M. Piorry[5] speaks out strongly for the use of iodine: "Since iodine succeeds in ordinary goiter . . . it is rational to give iodine in goiter with protrusion of the eyes. For it to succeed one must give sufficient." M. Piorry said he had obtained remarkable success by the use of this medicine in a case of exophthalmic goiter, whose picture he showed to the Academy and which it reproduced in the article. Trousseau,[6] in a report of a case of exophthalmic goiter, remarks "I treated her with preparations of iodine" and one gets the impression that he thought favorably of the result. In this connection one should mention the famous incident of Trousseau's mistake in using tincture of iodine when he meant to give tincture of digitalis.[7] "In . . . October 1863 a young lady . . . came to consult me. . . . She had a subacute form of exophthalmic goiter. . . . I repeated the examination on several occasions . . . and I always found that the heart beat 140-150 times a minute. . . . I wished her to take tincture of digitalis; but preoccupied with the danger of giving iodine, the name of this medicine came from my pen, and the patient, for 15 days, took 15 to 20 drops of tincture of iodine each day. She came back with a pulse of only 90. I perceived my error, replaced the tincture of iodine by tincture of digitalis, and fifteen days later found the pulse again 150. I hastened again to give her the tincture of iodine." But the great Trousseau evidently did not learn the lesson so obviously before him, because he continues "Be this as it may, gentlemen, remember well that iodine usually is harmful in treating Graves' disease."

Meanwhile M. Naumann[8] reports an equivocal experience in a case of swelling of the thyroid and exophthalmos. Iodine therapy was begun on Nov. 20, and by Dec. 5 the gland was smaller and at the same time the thrill and pulsation were markedly diminished. Naumann continued to prescribe iodine but by the middle of December was compelled to stop because of rapid growth of the gland and pain in the eyes. Here then we have a beautiful example of "iodine escape," a phenomenon observed and studied 75 years later.[29] Antoine Cros[9] alludes to a patient with definite exophthalmic goiter "who was notably helped, and whose goiter rapidly decreased in size under the influence of iodide of potassium internally," and Bouilland[10] in the same year, in a discussion of exophthalmic goiter, in defending iodine against attack, says "One can not conclude therefore that iron and iodine are inefficient; they are a great help."

It was W. B. Cheadle,[11] however, who first treated a series of cases in organized fashion and spoke unequivocally in favor of the beneficial effect of iodine. "The immediate and extraordinary improvement which followed the use of iodine . . . can hardly be referred to a coincidence in each instance of the administration of the remedy with the natural decline of the malady. The tolerance of this drug . . . shows that the statements made by nearly every writer on the subject . . . are not fully borne out by the facts . . . these records prove, I think, that it ought not to be excluded from the list of remedies available for the treatment of exophthalmic goiter." Later Cheadle[12] reiterated his claim; but he could get no serious attention, and praise of the use of iodine continued half-hearted, as in the case of Gros,[13] who says, "It is not the same with iodine, which Trousseau has proscribed as being bad medicine. However I have seen two cases in which iodine gave excellent results." None of the other seven doctors who discussed this paper mentioned iodine. Greenhow,[14] in a meeting at the Clinical Society of London, refers to a case in which there was given potassium iodide and syrup of the iodide of iron "with most beneficial results" but "change of air . . . also had a great deal to do with the cure." So too as late as 1891 W. H. Draper,[15] in New York, has seen in Graves' disease "the most beneficial results" from iodide of potassium "used on the principle that it markedly affects the heart's action," but F. Delafield, in the same discussion, was doubtful.

On the whole, then, one sees that iodine before the turn of the century achieved no real standing in the therapy of exophthalmic goiter, except perhaps with Cheadle, who made little if any impression on the medical public. Those who thought iodine harmful, however, spoke with a strong voice from the start.

As long ago as 1862 Hiffelsheim [16] reported the case of an 18-year-old girl who was "intolerant to iodine. The arterial beating became more pronounced in less than 15 days. I had to stop the iodide." In 1866 Oppolzer,[17] the Viennese professor of medicine, in a systematic discussion of Basedow's disease dismisses iodine with abruptness. The internal use of iodine "has not held up so that one should not waste time with trials of it." So too another influential voice, that of N. Friedreich,[18] in his textbook on diseases of the heart, states bluntly "a brisk internal course of iodine therapy is contraindicated under all circumstances." Morrell Mackenzie,[19] the great English laryngologist, reported four cases. In the first he used iodine. "She considered it did her a great deal of good but complained of its producing a feeling of great coldness, so that she was unable to continue it." Mackenzie was evidently discouraged, since nothing is said of iodine in the other three cases. Bämler,[20] also, reports a classical case of Graves' disease which he treated with potassium iodide internally; but he was forced to stop because of an attack of palpitation, although he points out that this was not definitely connected with the use of iodide "even if the susceptibility of such patients to potassium iodide is as great as Trousseau insists." Rendu,[21] however, told of a patient who while under treatment with iodide for "aortitis" developed "great nervousness, exophthalmos, palpitation . . . all phenomena indicating development of Basedow's disease," and Sée,[22] in a pharmacological consideration of the action of potassium iodide on the heart, concluded that Basedow's disease which stems from a paralysis of the inhibitory nerves "can draw no benefit from the action of iodine." Buschan,[23] in his monograph, after going over all the evidence gives a feeble explanation of the contradictory results of iodine by suggesting that favorable effects occurred in cases of the "symptomatic form of Basedow," whereas failures resulted in the "genuine form," but it remained for Moebius,[24] the great German student of Basedow's disease, to give the *coup de grâce* to iodine. "It is settled that iodine is never to be used in Basedow's disease; its use is to be warned against."

H. Sattler, the ophthalmologist whose monograph is a landmark in the subject,[25] discussed the question of acute hyperthyroidism following the use of iodine in Basedow's disease and reported a number of cases. In the same year T. Kocher,[26] the great thyroid surgeon of Berne, wrote a paper on iodine exophthalmic goiter ("Jodbasedow") which had an immense influence on the use of iodine in exophthalmic goiter. Kocher, who actually was confused by the frequency of simple goiter in Berne and the difficulty of always making a clear differentiation from Basedow's disease, concluded: "Iodine medication remains a two edged sword which acts both ways in Basedow, and in practice the harm caused by iodine in all typical and atypical forms is much greater than the benefit." It must be admitted that some of the poor results and apparent iodine exacerbations seen by these keen observers were probably instances of "iodine escape," but the oracle had finally spoken, and it was not until Henry Plummer had the fortitude to reintroduce the use of iodine in Graves' disease over 30 years later that the ghost of Kocher's doctrine was laid.†

Plummer and Boothby [27] broke all the rules and boldly gave large amounts of iodine to patients with hyperthyroidism. The course under iodine is described: There was prompt alleviation of toxic symptoms, fall in basal metabolic rate, and, above all, it became

† Dr. Halsted, a great frind of Kocher and strongly influenced by him, was so terrified lest a patient with Graves' disease be exposed even to a whiff of iodine that he had iodoform, a popular antiseptic, barred from his operating room.

possible to do thyroidectomy without bringing on the dreaded thyroid crisis.[28] This paper is purely descriptive; Plummer states that a discussion of theories leading up to the trial of iodine was given at the meeting of the Association of American Physicians in June, 1923. An inspection of the Transactions of the Association for 1923, however, shows nothing by Plummer, but, curiously enough, under the heading "American Association of Physicians" there appears (*J. A. M. A.* 80:1955, 1923) a brief note by Dr. H. S. Plummer entitled "Results of Administering Iodin to Patients Having Exophthalmic Goiter." After some obscure preliminary remarks Plummer says: "Acting on this plan, we administered 10 drops of compound solution of iodin for ten days *following* operation [italics ours], with the result that we have found there is no such thing as postoperative deaths from hyperthyroidism if this dosage has been administered to the patient with regularity. In other words, the patient is relatively short of iodin, and dies from lack of it. When we replace the iodin, we do away with postoperative deaths." But in 1924, in the discussion of a paper by E. H. Mason (Iodine Therapy in Toxic Goiter, *Tr. A. Am. Physicians* 33:178, 1924), Plummer, that strange genius, gives an unintelligible statement of his rationale: "The symptom-complex of exophthalmic goiter is the result of intensive stimulation of the thyroid. Under intense stimulation of the thyroid two products are developed. A normal and an abnormal product is delivered to the tissues. The symptom-complex varies with the total amount of the product and the relative amount of each product. . . . Under the stimulation the thyroid becomes trained. A well trained thyroid can produce a large amount of a normal product. Intensive stimulation of an untrained gland produces a large amount of an abnormal product. If the basal metabolism is +80 from the normal product, Lugol's solution has little effect."

Now in the light of present knowledge there was no rational basis for this statement, so it turns out that Plummer's radical views, while invaluable, were really based on unsound premises. The history of medicine shows many examples of "inspirations" which turned out to be correct, beginning with no less a figure than Jenner and the introduction of vaccination.

But the use of iodine in Graves' disease did not immediately receive unqualified approval. Henry Christian, for example, opened the discussion of Mason's paper with a strong note of caution: "I suspect that a great deal of damage is going to be done with iodine to the thyroid cases if we get too enthusiastic over these results. Our results in Boston . . . have shown that iodine is very valuable as a preparation for operation, because it controls the situation temporarily in certain cases. Our experience is that the control is limited, and continuation of treatment in a large percentage of cases seems to result in a later loss of benefit from the iodine. If it is discontinued there may be a marked increase in symptoms. In both events metabolism is apt to swing to a point which is much higher than that prior to the iodine therapy. Consequently, there is considerable danger in connection with operations, if iodine is omitted too soon and apparently sometimes even if not omitted, because it has been given so long as to lose its effect."

So entrenched did this view become that it was customary in many large hospitals not to start iodine in Graves' disease until the patient had given written permission for operation when the appropriate point was reached after about two weeks and a maximum lowering of basal metabolism with abatement of symptoms had taken place. One did not dare to leave the iodinized patient unoperated on, so great was the fear of "iodine escape." Means[29] has tried to explain this phenomenon on the basis of spontaneous fluctuations in the severity of the disease. He believes that cessation of iodine simply unmasks an exacerbation which may become evident in spite of iodine. Means drew charts for this paper, which were reproduced in his book years later.[30]

But whether or not Means' explanation is correct, it is hard to believe that such keen observers as Trousseau, Friedreich, Sattler, Moebius, and Kocher were scared away from the use of iodine without good reason. Whatever the explanation it is certain that many patients with Graves' disease treated with iodine and without operation at the peak of the iodine remission become much worse, and it was clearly this observation, made over and over again, which impelled these wise old physicians to caution.

At any rate the facts brought out by Plummer were promptly confirmed by many observers, such as Boothby [31] and Starr and his colleagues,[32] and until the advent of thiouracil iodine remained invaluable in preoperative preparation of cases of Graves' disease. Although the "involuting" effect of iodine on the thyroid had already been stressed by Marine and Williams,[33] it remained for Rienhoff [34] to prove this. Rienhoff secured biopsy specimens of the thyroid from cases of exophthalmic goiter and after treatment with iodine did thyroidectomy. The sections from the same patient before and after iodine present a sharp contrast: before, the typical hyperplastic gland of Graves' disease; after, the picture of involution, with wide vesicles, flat epithelium, and abundant colloid.

What then is the explanation of the action of iodine in Graves' disease? Rawson,[35] using iodine when the gland had been rendered hyperplastic but hypofunctioning by the administration of thiouracil, seemed to show that iodine exerted both an iodinating and an involuting effect; the whole question is further discussed, recently, by Dobyns.[36]

But my task has been to tell the story of the use of iodine in Graves' disease, and the final answers as to its mechanism of action I leave to others.

Stanford University School of Medicine, 2398 Sacramento St. (15).

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Epilepsy: Grand Mal, Petit Mal, Convulsions. By Letitia Fairfield, C.B.E., M.D., D.P.H. Price, $4.75. Pp. 159. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1957.

Popular misunderstanding about epilepsy is so general that a book which details certain facts clearly and succinctly serves a useful purpose. Dr. Fairfield has met this need. The first third of her small book deals with diagnosis and treatment, and the remainder is concerned with the subjects of schooling, employment, colonies for the epileptic, and various laws as these relate to patients. In Great Britain, socialized medicine provides some aids to social treatment, such as the Medical Officer of Health, the Disablement Resettlement Officer, and the Youth Employment Service. Although companies are required to employ a certain number of handicapped persons, they can and do discriminate against the epileptic.

WILLIAM G. LENNOX, M.D.

Physiologic Principles of Surgery. Edited by L. M. Zimmerman and R. Levine. Price, $15. Pp. 988, with 112 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1957.

This volume represents a serious effort to assemble the physiologic problems associated with surgical diseases, including the changes accompanying their operative approach. It covers a wide range, including the changes resulting from various injuries; infections and antibiotics; nutrition; blood; electrolytes; tissue transplantation; anesthesia; gastrointestinal, respiratory, and genitourinary tracts; endocrine glands, and the cardiovascular, reproductive, central nervous, and locomotor systems.

In this, as in other books of the multiple-author type, a minor defect is occasional repetition in different chapters. This is unavoidable, as the authors cover each subject heading thoroughly. Some chapters are well written and very readable; others are cumbersome.

In certain small areas I might disagree with statements made, but on the whole the authors have done a remarkable job of presenting a wealth of information, often of difficult and conflicting material. The volume should prove of great value to the resident in surgery, to the practicing surgeon, and occasionally to others as a reference volume.

S. E. ZIFFREN, M.D.

Grundriss der inneren Medizin. By Dr. Hans von Kress. Twenty-second edition. Price, 39 marks. Pp. 699, with 47 illustrations. Springer-Verlag, Reichpietschufer 20, (1) Berlin W. 35, 1957.

This is the twenty-second edition of a manual written primarily for the use of medical students. The large number of editions since its first publication by Domarus, in 1923, seems to indicate its popularity in Germany.

To the American reader this book has a number of confirming aspects, a few of which should be pointed out.

The German "Die Rheumatoide" (p. 574), under the general heading of diseases of the joints, has nothing to do with our concept of rheumatoid arthritis. "Rheumatoide" are, rather, afilictions of the joints secondary to scarlet fever and other infectious diseases. Also, joint involvements after serum injections are taken into this group.

Strümpell-Pierre-Marie's disease is viewed as caused by infection. Consequently, it is torn out of the American concept of rheumatoid arthritis, which, by the way, is named "chronic polyarthritis" and not considered a collagen disease.

The collagen diseases as an entity are given short-shrift treatment in a chapter filling only one page (p. 580). This is surprising, in view of the growing importance of this group of diseases during the last decade.

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmissal to him.

Also surprising is the recommendation of Pyramidon in the therapy of rheumatic fever (the term acute polyarthritis is preferred in the German nomenclature). Pyramidon is supposed to be given in large daily doses, of 5 to 10 gm. However, one has to keep in mind that this drug, virtually taboo in this country, can be purchased "over the counter" without a prescription everywhere on the European continent.

On the other hand, the authors do not mention the long-term protection of patients with rheumatic fever with penicillin, so widely and successfully used in this country.

On the credit side of the book shines the excellent chapter on neurological diseases. It is outstanding in systematic clarity and painstaking detail.

Paper, print, and reproduction of pictures are satisfactory but below the standard of pre-World War II publications of the Springers.

ERICH STERN, M.D.

News and Comment

ANNOUNCEMENTS

Awards for Advanced Nurse Training.—The Department of Health, Education, and Welfare has announced that 587 awards for advanced nurse training have been made under a new Public Health Service program.

The Service has just completed allocation of $2,000,000 appropriated by Congress last August to help overcome a serious shortage of nurses trained for teaching, supervisory, and administrative positions. This appropriation was for the first year of an authorized three-year program.

The funds have been made available through 56 schools of nursing and public health to assist nurse trainees from every state.

Half of this year's trainees are preparing for teaching positions. Twenty-eight per cent are training for administrative posts, and the remaining twenty-two per cent, for supervisory positions.

A preference for positions in schools of nursing or practical nursing was indicated by 56% of the trainees. Twenty-eight per cent said they prefer hospital nursing service, and sixteen per cent plan to work in public health.

Correction

In the article "Infections Due to Bacterium Anitratum," by Drs. Heonir Rocha and Lucien B. Guze, in the August issue of THE ARCHIVES (pp. 272-275), the graphs for Figures 1 and 2 are interchanged.

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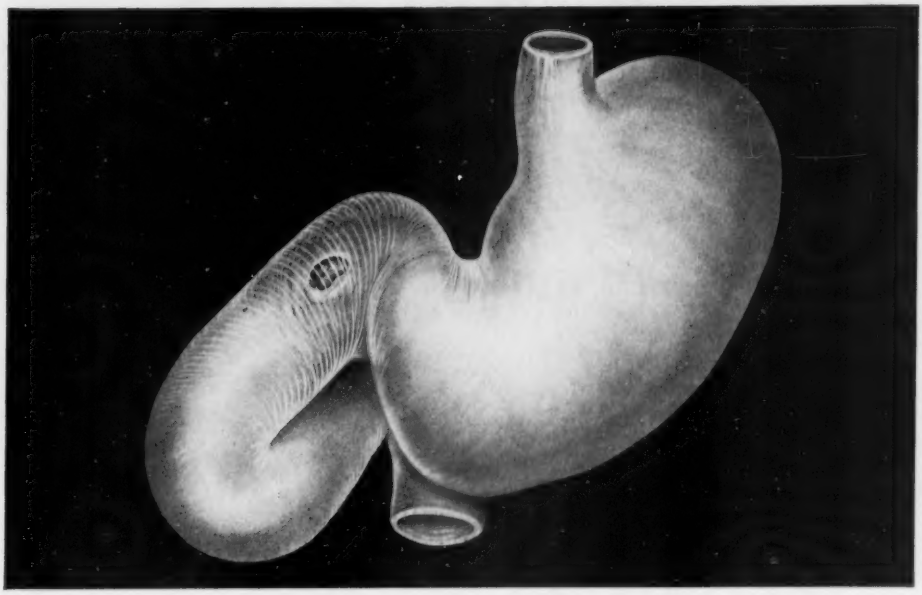

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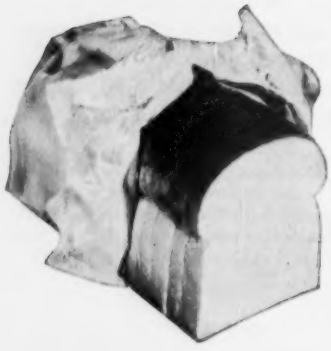

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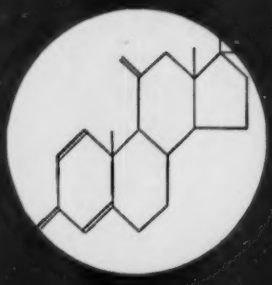

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Quarterly Cumulative Index Medicus

WITH AUTHORS AND SUBJECTS . . .

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Finch, J.W.: Clinical Trial of Orphenadrine (Disipal) in Skeletal Muscle Disorders. To be published.

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INDICATIONS

Parkinsonism

•

Muscle spasm due to

- Sprains
- Strains
- Herniated intervertebral disc
- Fibrositis
- Low back pain
- Whiplash injuries
- Noninflammatory rheumatic and arthritic states
- Torticollis

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Doshay, L.J., and Constable, K.: Treatment of Paralysis Agitans with Orphenadrine (Disipal) Hydrochloride: Results in One Hundred Seventy-Six Cases, J.A.M.A. 163:1352 (Apr. 13) 1957.

Dosage: 1 tablet (50 mg.) t.i.d. In Parkinsonism, when used in combination with other drugs, smaller dosage may suffice.

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supplied: 300 mg. scored tablets, bottles of 48 and 500.

(1) Asung, C. L.; Charcowa, A. I., and Villa, A. P.: Sea View Hosp. Bull. *16*:80, 1956. (2) Asung, C. L.; Charcowa, A. I., and Villa, A. P.: New York J. Med. *57*:1911 (June 1) 1957. (3) Report on Field Screening of Nostyn by 99 Physicians in 1,000 Patients, June, 1956.

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